# Conversion of (+)-8,11,13-Abietatriene into (15*R*)-16-Hydroxyferruginol and Its (15*S*)-Epimer

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**Synopsis.** (+)-8,11,13-Abietatriene was converted into (15*R*)-16-hydroxyferruginol (**1a**) and its (15*S*)-epimer (**1b**) by the introduction of hydroxyl groups at the C-12 and C-16 positions.

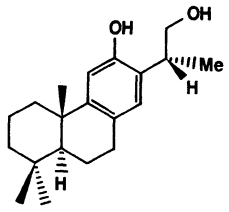
16-Hydroxyferruginol has been isolated from the seed of *Thujopsis dolabrata* Sieb. et Zucc. var *dolabrata* by Hasegawa and Hirose.[1] In a previous paper,[2] we reported the total syntheses of (15*R*)-16-hydroxyferruginol (**1a**) and its (15*S*)-epimer (**1b**), and determined the absolute configuration of the C-15 position in the natural compound to be the *R*-configuration. These C-15 epimeric 16-hydroxyferruginols (**1a** and **1b**) are also useful intermediates for the syntheses of highly-oxygenated abietane-type diterpenes possessing an asymmetric center at the C-15 position such as (15*R*)-coleon C (**2a**),[3,4] (15*S*)-coleon C (**2b**),[3,4] lycoxanthol (**3**),[5,6] nellionol,[7] hyptol,[8] and so on. As an extension of our previous work, we describe here the syntheses of **1a** and **1b**, starting from natural (+)-8,11,13-abietatriene (**4**) as an optically-active relay compound.

Dehydrogenation of **4** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing 1,4-dioxane afforded the corresponding isopropenyl compound (**5**) which was immediately submitted to hydroboration–oxidation and the resulting C-15 epimeric mixture of 8,11,13-abietatrien-16-ols (**6**: 33% yield from **4**) was further converted into 4-nitrobenzoates (**7**: 93% yield) by heating with 4-nitrobenzoyl chloride in pyridine. The Friedel-Crafts acylation of **7** with acetyl chloride and anhydrous aluminium chloride in nitrobenzene afforded a C-15 epimeric mixture (*ca.* 1:1 ratio) of 12-acetyl compounds (**8a,b**) in a 63% yield. This mixture of **8a,b** was carefully separated by repeated column chromatography and recrystallization to give pure crystalline (15*R*)-12-acetyl-16-(4-nitrobenzoyloxy)-8,11,13-abietatriene (**8a**), mp 139—142 °C, and its (15*S*)-epimer (**8b**), mp 166—167 °C. The Baeyer–Villiger oxidations of **8a** and **8b** with *m*-chloroperbenzoic acid and *p*-toluenesulfonic acid in refluxing 1,2-dichloroethane, followed by reductions of the resulting acetates, **9a** (59% yield) and **9b** (70% yield), with lithium aluminium hydride in dry ether afforded the desired **1a** (90% yield) and **1b** (97% yield), respectively. The physical and spectral data of the synthetic **1a** and **1b** were identical with those of authentic (15*R*)-16-hydroxyferruginol and its (15*S*)-epimer,[2] respectively.

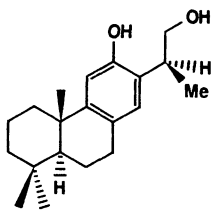
## Experimental

All melting points are uncorrected. The IR spectra and optical rotations were measured in chloroform. The column chromatography was performed using Merck silica gel (0.063 mm).

**16-(4-Nitrobenzoyloxy)-8,11,13-abietatriene (7).** A mixture of (+)-8,11,13-abietatriene (**4**) (26.00 g) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (96%: 26.20 g) in 1,4-dioxane (260 ml) was refluxed for 4 h. The mixture was passed through an alumina (Merck Act. II-III, 220 g) column and the column was washed with benzene (800 ml). The eluate was evaporated in vacuo to give a crude 8,11,13,15-abietatetraene



**1a**



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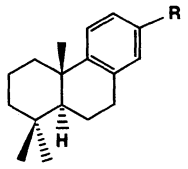
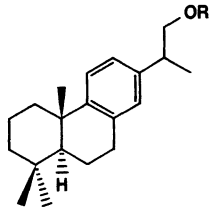
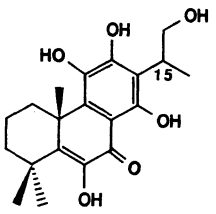


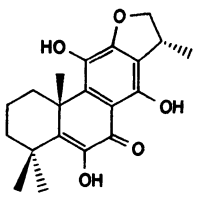
**4** R=CHMe2
**5** R=C(Me)=CH2



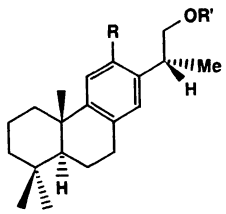
**6** R=H
**7** R=COC6H4NO2(p)

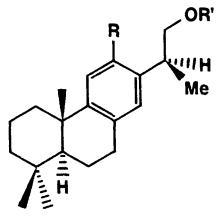


**2a** 15R
**2b** 15S



**3**



**8a** R=Ac, R'=COC6H4NO2(p) **8b**
**9a** R=OAc, R'=COC6H4NO2(p) **9b**

(**5**) (23.358 g), $^1$H NMR (60 MHz, $CCl_4$) $\delta$=0.93 (6H, s, $-C(CH_3)_2$), 1.14 (3H, s, 10-$CH_3$), 2.07 (3H, bs, 15-$CH_3$), 4.87 (1H, bs) and 5.17 (1H, bs) ($-C(CH_3)=CH_2$).

A solution of tetrahydrofuran–borane (1/1) addition compound (1 mol dm$^{-3}$: 43.5 ml) was added to a stirred solution of the crude **5** (23.358 g) in dry tetrahydrofuran (200 ml) at −15 to −10 °C for 30 min under a stream of nitrogen. After the mixture was stirred at 0—5 °C for 3 h, the following compounds were added successively: aqueous tetrahydrofuran (50%: 15.5 ml), aqueous sodium hydroxide (12%: 15.5 ml), and hydrogen peroxide (30%: 15.5 ml) at −15 to −5 °C. The mixture was stirred at −5—0 °C for 30 min and then at room temperature for 1.5 h, diluted with brine, 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 (0.063—0.200 mm, 250 g), using benzene as an eluent, to give mainly recovered **4** (11.91 g). Further elution with benzene afforded a mixture of the C-15 epimeric 8,11,13-abietatrien-16-ols (**6**) (9.116 g: 33.1% yield from **4**), IR 3580 and 3425 cm$^{-1}$, $^1$H NMR (60 MHz, $CCl_4$) $\delta$=0.95 (6H, s, $-C(CH_3)_2$), 1.15 (3H, s, 10-$CH_3$), 1.18 (3H, d, $J$=7 Hz, 15-$CH_3$), 3.45 (2H, d, $J$=7 Hz, $-CH_2OH$), 6.72 (1H, bs, 14-H), 6.80 (1H, bd, $J$=8 Hz, 12-H), and 7.05 (1H, d, $J$=8 Hz, 11-H).

A mixture of compound **6** (2.755 g) and 4-nitrobenzoyl chloride (2.678 g) in pyridine (14 ml) was heated at 80—85 °C for 2.5 h. After the usual work-up, the crude product was recrystallized from hexane to give a C-15 epimeric mixture of **7** (1.936 g: 46.2% yield), mp 97—98 °C, IR 1720 cm$^{-1}$. Found: C, 74.48; H. 7.84; N, 2.94%. Calcd for $C_{27}H_{33}O_4N$: C, 74.45; H, 7.64; N, 3.22%. The mother liquor of recrystallization was evaporated in vacuo. The residue was chromatographed on silica gel (20 g), using hexane–benzene (1:1) as an eluent, to give additional **7** (1.956 g: 46.7% yield).

**(15R)-12-Acetyl-16-(4-nitrobenzoyloxy)-8,11,13-abietatriene (8a) and Its (15*S*)-Epimer (8b).** Anhydrous aluminium chloride (2.370 g) was added at 0—5 °C to a stirred solution of **7** (1.936 g) and acetyl chloride (1.30 ml) in nitrobenzene (12 ml). The mixture was stirred at this temperature for 30 min and then at room temperature for 1.5 h, then poured into ice-dilute hydrochloric acid and extracted with ether. The ether extract was washed with aqueous sodium hydrogencarbonate and brine, dried, and evaporated in vacuo. The residue was chromatographed on silica gel (100 g), using hexane–benzene (3:7) as an eluent, to give a mixture (ca. 1:1 ratio) of **8a** and **8b** (1.331 g: 62.7% yield). This mixture was separated into pure **8a** and **8b** by repeated column chromatography and recrystallization.

**8a**: Mp 139—142 °C (from acetone–hexane), $[\alpha]_D$+42.7° (*c* 1.34), IR 1722 and 1675 cm$^{-1}$; $^1$H NMR (90 MHz, $CCl_4$) $\delta$=0.93 (6H, s, $-C(CH_3)_2$), 1.18 (3H, s, 10-$CH_3$), 1.32 (3H, d, $J$=7 Hz, 15-$CH_3$), 2.50 (3H, s, $-COCH_3$), 3.97 (1H, m, 15-H), 4.36 (2H, d, $J$=7 Hz, 15-$CH_2O$–), 7.00 (1H, s, 14-H), 7.43 (1H, s, 11-H), 8.07 (2H, d, $J$=10 Hz) and 8.21 (2H, d, $J$=10 Hz) ($-C_6H_4NO_2$). Found: C, 72.74; H, 7.60; N, 2.65%. Calcd for $C_{29}H_{35}O_5N$: C, 72.93; H, 7.39; N, 2.93%.

**8b:** Mp 166—167 °C (from acetone–hexane), $[\alpha]_D$+35.0° (*c* 2.86), IR 1725 and 1680 cm$^{-1}$; $^1$H NMR (90 MHz, $CCl_4$) $\delta$=0.93 (3H, s) and 0.95 (3H, s) ($-C(CH_3)_2$), 1.18 (3H, s, 10-$CH_3$), 1.30 (3H, d, $J$=7 Hz, 15-$CH_3$), 2.49 (3H, s, $-COCH_3$), 3.97 (1H, m, 15-H), 4.40 (2H, d, $J$=7 Hz, 15-$CH_2O$–), 7.00 (1H, s, 14-H), 7.43 (1H, s, 11-H), 8.08 (2H, d, $J$=10 Hz) and 8.22 (2H, d, $J$=10 Hz) ($-C_6H_4NO_2$). Found: C, 72.70; H, 7.61; N, 2.79%. Calcd for $C_{29}H_{35}O_5N$: C, 72.93; H, 7.39; N, 2.93%.

**(15*R*)-12-Acetoxy-16-(4-nitrobenzoyloxy)-8,11,13-abietatriene (9a) and Its (15*S*)-Epimer (9b).** a): A mixture of **8a** (110.0 mg), *m*-chloroperbenzoic acid (80%: 99.4 mg), and *p*-toluenesulfonic acid (10.0 mg) in 1,2-dichloroethane (1.5 ml) was refluxed for 3 h. The mixture was cooled, diluted with ether, and the ether solution was washed successively with aqueous potassium iodide, aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate, and brine. The dried solution was evaporated in vacuo. The residue was chromatographed on silica gel (5 g), using benzene as an eluent, to give **9a** (67.4 mg: 59.3% yield) which was recrystallized from methanol, mp 110—113 °C, $[\alpha]_D$+67.4° (*c* 1.41), IR 1758 and 1725 cm$^{-1}$. Found: C, 70.26; H, 7.33; N, 2.54%. Calcd for $C_{29}H_{35}O_6N$: C, 70.56; H, 7.15; N, 2.84%.

b): A mixture of **8b** (358.0 mg), *m*-chloroperbenzoic acid (80%: 324.0 mg), and *p*-toluenesulfonic acid (20.0 mg) in 1,2-dichloroethane (3.5 ml) was treated as described in a). The crude product was chromatographed on silica gel (15 g), using benzene as an eluent, to give **9b** (259.6 mg: 70.2% yield) which was recrystallized from acetone–methanol, mp 114—116 °C, $[\alpha]_D$+11.8° (*c* 2.64), IR 1755 and 1725 cm$^{-1}$. Found: C, 70.70; H, 7.35; N, 2.65%. Calcd for $C_{29}H_{35}O_6N$: C, 70.56; H, 7.15; N, 2.84%.

**(15*R*)-16-Hydroxyferruginol (1a) and Its (15*S*)-Epimer (1b).** a): A mixture of **9a** (51.0 mg) and lithium aluminium hydride (20.0 mg) in dry ether (1.5 ml) was stirred at room temperature for 1.5 h. The mixture was poured into ice-dilute hydrochloric acid and extracted with ether. The ether extract was washed with brine, dried, and evaporated in vacuo. The residue was chromatographed on silica gel (5 g), using ether–benzene (8:92) as an eluent, to give **1a** (28.1 mg: 90.1% yield) which was recrystallized from acetone–hexane, mp 138—139 °C, $[\alpha]_D$+64.9° (*c* 0.96), IR 3600 and 3325 cm$^{-1}$, $^1$H NMR (90 MHz, $CDCl_3$) $\delta$=0.89 (3H, s), and 0.91 (3H, s), ($-C(CH_3)_2$), 1.13 (3H, s, 10-$CH_3$), 1.24 (3H, d, $J$=7 Hz, 15-$CH_3$), 3.15 (1H, m, 15-H), 3.64 (1H, dd, $J$=10 and 7.5 Hz) and 3.88 (1H, dd, $J$=10 and 4 Hz) (15-$CH_2OH$), and 6.72 (2H, s, 11-H and 14-H). Found: C, 79.31; H, 10.28%. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00%.

b): A mixture of **9b** (179.9 mg) and lithium aluminium hydride (70.0 mg) in dry ether (4.0 ml) was treated as described in a). The crude product was chromatographed on silica gel (5 g), using ether-benzene (8:92) as an eluent, to give **1b** (107.0 mg: 97.1% yield) which was recrystallized from acetone–hexane, mp 179—180 °C, $[\alpha]_D$+ 46.0° (*c* 1.37), IR (KBr) 3550 and 3270 cm$^{-1}$, $^1$H NMR (90 MHz, $CDCl_3$) $\delta$=0.91 (6H, s, $-C(CH_3)_2$), 1.16 (3H, s, 10-$CH_3$), 1.26 (3H, d, $J$=7 Hz, 15-$CH_3$), 3.15 (1H, m, 15-H), 3.64 (1H, dd, $J$=10 and 7 Hz) and 3.88 (1H, dd, $J$=10 and 4 Hz) (15-$CH_2OH$), and 6.74 (2H, s, 11-H and 14-H). Found: C, 79.28; H, 10.23%. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00%.

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