The Synthesis of Hyptol and Its C-15 Epimer from (+)-Dehydroabietic Acid

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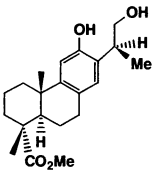
In order to elucidate the absolute configuration of C-15 in natural hyptol, methyl (15*S*)-12,16-dihydroxy-8,11,13-abietatrien-18-oate and its (15*R*)-epimer were transformed into (15*S*)-12,16-epoxy-11,14-dihydroxy-8,11,13-abietatrien-7-one (**1a**) and its (15*R*)-epimer (**1b**), respectively. The synthetic **1a** was identical to natural hyptol. Thus, the stereochemistry of C-15 in the natural compound was conclusively assigned as *S*-configuration.

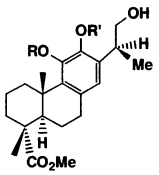
Hyptol, a rare abietane-type diterpene possessing a dihydrofuran moiety, has been isolated from the roots of *Hyptis fructicosa* (Labiatae) by Monache et al.[1] On the basis of chemical and spectroscopic studies, they deduced the structure of hyptol to be 12,16-epoxy-11,14-dihydroxy-8,11,13-abietatrien-7-one (**1**). However, the absolute configuration of the C-15 position in the natural compound remained unsolved. In order to elucidate the unknown stereochemistry at the C-15 position, we have attempted the syntheses of (15*S*)-12,16-epoxy-11,14-dihydroxy-8,11,13-abietatrien-7-one (**1a**) and its (15*R*)-epimer (**1b**). For this purpose, methyl (15*S*)-12,16-dihydroxy-8,11,13-abietatrien-18-oate (**2a**)[2] and its (15*R*)-epimer (**2b**)[2] were chosen as convenient relay intermediates, because these compounds have recently been synthesized in our laboratory starting from (+)-dehydroabietic acid.

To introduce an oxygen function at the C-11 position, the (15*S*)-12,16-dihydroxy compound (**2a**) was refluxed with benzoyl peroxide in chloroform to give a mixture of methyl 11-benzoyloxy-12,16-dihydroxy-8,11,13-abietatrien-18-oate (**3a**) and its 12-benzoyloxy-11,16-dihydroxy isomer (**4a**) (ca. 1:1 ratio) in a 36% yield. The mixture of **3a** and **4a** was further transformed into a dihydrobenzofuran compound (**5a**: 70% yield) by a series of reactions: mesylation with methanesulfonyl chloride in pyridine, refluxing with sodium iodide in ethyl methyl ketone, and treatment with aqueous sodium hydroxide in refluxing methanol. Reduction of **5a** with lithium aluminum hydride in ether followed by mesylation of the resulting alcohol (**6a**) with methanesulfonyl chloride in pyridine afforded a mesylate (**7a**). This was treated with sodium iodide and zinc powder in *N*,*N*-dimethylformamide at 120—125 °C to give a 4,4-dimethyl compound (**8a**) in a 56% yield from **5a**. Oxidation of **8a** with Fremy's salt and potassium dihydrogenphosphate in aqueous *N*,*N*-dimethylformamide afforded a para-quinone (**9a**) in an 80% yield. This was submitted to reductive acetylation with zinc powder and acetic anhydride in pyridine to give a diacetate (**10a**: 94% yield), which was further oxidized with chromium trioxide in acetic acid to give a ketone (**11a**: 72% yield). Hydrolysis of **11a** with dilute hydrochloric acid in refluxing ethanol afforded the desired (15*S*)-hyptol (**1a**: 98% yield), the physical and spectral data of which were identical to those of natural hyptol.

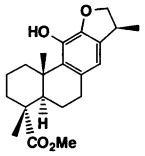
For direct comparison with **1a**, the synthesis of (15*R*)-hyptol (**1b**) was also carried out in the same manner as that described for the preparation of **1a**. Oxidation of the (15*R*)-12,16-dihydroxy compound[2] (**2b**) with benzoyl peroxide in refluxing chloroform produced a mixture of methyl 11-benzoyloxy-12,16-dihydroxy-8,11,13-abietatrien-18-oate (**3b**) and its 12-benzoyloxy-11,16-dihydroxy isomer (**4b**) (ca. 1:1 ratio, 38% yield). This mixture was converted into a dihydrobenzofuran compound (**5b**), which was further transformed into a para-quinone (**9b**) via an alcohol (**6b**), a mesylate (**7b**), and a 4,4-dimethyl compound (**8b**). Reductive



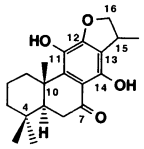
2a



3a R=Bz, R'=H
4a R=H, R'=Bz



5a



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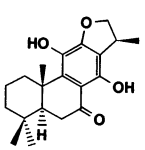
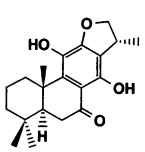
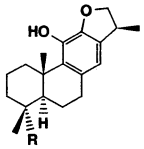


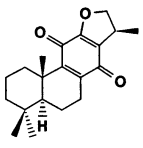
1a



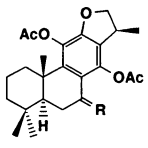
1b



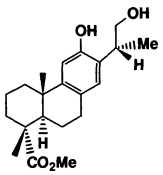
6a R=CH2OH
7a R=CH2OMs
8a R=Me



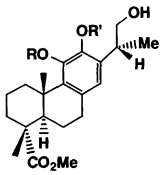
9a



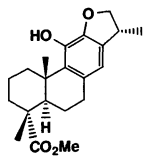
10a R=H2
11a R=O



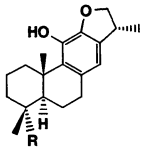
2b



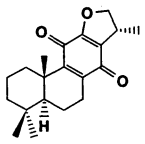
3b R=Bz, R'=H
4b R=H, R'=Bz



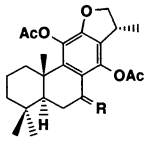
5b



6b R=CH2OH
7b R=CH2OMs
8b R=Me



9b



10b R=H2
11b R=O

acetylation of **9b** followed by oxidation of the resulting diacetate (**10b**) afforded a ketone (**11b**). This was hydrolyzed with dilute hydrochloric acid in refluxing ethanol to give (15*R*)-hyptol (**1b**). The physical and spectral data of the synthetic **1b** were not identical to those of natural hyprol.

From the present study, the stereochemistry of the C-15 position in natural hyptol was conclusively assigned as *S*-configuration.

Experimental

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

Oxidation of Methyl (15*S*)-12,16-Dihydroxy-8,11,13-abietatrien-18-oate (2a) and Its (15*R*)-Epimer (2b) with Benzoyl Peroxide. a): A solution of **2a**[2] (1.852 g) and benzoyl peroxide (1.944 g) in chloroform (21 ml) was gently refluxed for 3.5 h. After the addition of ether (30 ml) acetic acid (14 ml), and aqueous potassium iodide (20%, 60 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. The residue was chromatographed on silica gel (25 g), using ether–benzene (5:95) as an eluent, to give a mixture of methyl 11-benzoyloxy-12,16-dihydroxy-8,11,13-abietatrien-18-oate (**3a**) and its 12-benzoyloxy-11,16-dihydroxy isomer (**4a**) (902 mg: 36.1% yield). IR 3575, 3300, 1737 sh, and 1723 cm^{-1}. ^{1}H NMR of **3a** (60 MHz) δ=1.19 and 1.28 (each 3H and s, 4-CH_3 and 10-CH_3), 3.64 (3H, s, $-CO_2CH_3$), 6.63 (1H, s, 14-H), and 7.3—7.7 (3H, m) and 8.18 (2H, bd, J=7 Hz) ($-C_6H_5$). ^{1}H NMR of **4a** (60 MHz) δ=1.24 and 1.30 (each 3H and s, 4-CH_3 and 10-CH_3), 3.64 (3H, s, $-CO_2CH_3$), 6.50 (1H, s, 14-H), and 7.3—7.7 (3H, m) and 8.18 (2H, bd, J=7 Hz) ($-C_6H_5$). Found: C, 72.37; H, 7.08%. Calcd for $C_{28}H_{34}O_6$: C, 72.08; H, 7.35%.

b): A solution of **2b**[2] (2.532 g) and benzoyl peroxide (2.657 g) in chloroform (28 ml) was gently refluxed for 3.5 h. After the work-up as described in a), the crude product was chromatographed on silica gel (25 g), using ether–benzene (5:95) as an eluent, to give a mixture of methyl 11-benzoyloxy-12,16-dihydroxy-8,11,13-abietatrien-18-oate (**3b**) and its 12-benzoyloxy-11,16-dihydroxy isomer (**4b**) (1.310 g: 38.4% yield). IR 3575, 3435, 1735 sh, and 1720 cm^{-1}. ^{1}H NMR of **3b** δ=1.21 and 1.30 (each 3H and s, 4-CH_3 and 10-CH_3), 3.63 (3H, s, $-CO_2CH_3$), 6.64 (1H, s, 14-H), and 7.4—7.7 (3H, m) and 8.18 (2H, dd, J=8 and 2 Hz) ($-C_6H_5$). ^{1}H NMR of **4b** δ=1.26 and 1.33 (each 3H and s, 4-CH_3 and 10-CH_3), 3.65 (3H, s, $-CO_2CH_3$), 6.53 (1H, s, 14-H), and 7.4—7.7 (3H, m) and 8.18 (2H, dd, J=8 and 2 Hz) ($-C_6H_5$). Found: C, 72.22; H, 7.57%. Calcd for $C_{28}H_{34}O_6$: C, 72.08; H, 7.35%.

Methyl (15*S*)-12,16-Epoxy-11-hydroxy-8,11,13-abietatrien-18-oate (5a) and Its (15*R*)-Epimer (5b). a): Methanesulfonyl chloride (0.19 ml) was added to a stirred solution of a mixture of **3a** and **4a** (ca. 1:1 ratio, 955 mg) in pyridine (2.0 ml) at 0—5 °C. The mixture was stirred at this temperature for 30 min and then at room temperature for 3 h, then poured into ice-dilute hydrochloric acid and extracted with ether. The ether extract was washed successively with aqueous sodium hydrogencarbonate and brine, dried, and evaporated in vacuo to give a mixture of mesylates (1.111 g).

A stirred mixture of the above crude mesylates (1.111 g) and sodium iodide (612 mg) in ethyl methyl ketone (22 ml) was refluxed for 4 h. The mixture was cooled, diluted with ether, and washed successively with water, aqueous sodium thiosulfate, and brine. The dried solution was evaporated in vacuo to give a mixture of iodides (1.160 g).

A mixture of the above crude iodides (1.160 g) and aqueous sodium hydroxide (20%, 2.9 ml) in methanol (14 ml) was refluxed for 1 h. After removal of the methanol in vacuo, the residue was acidified with 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 (25 g), using hexane–benzene (3:7) as an eluent, to give **5a** (478 mg: 69.5% yield), mp 155.5—157 °C (from hexane), $[\alpha]_D$+65.9 ° (c 0.41), IR 3560, 3375, and 1720 cm^{-1}; ^{1}H NMR δ=1.25 and 1.32 (each 3H and s, 4-CH_3 and 10-CH_3), 1.27 (3H, d, J=7 Hz, 15-CH_3) 3.66 (3H, s, $-CO_2CH_3$), 4.03 (1H, t, J=8 Hz) and 4.68 (1H, t, J=8 Hz) (15-CH_2O–), 4.87 (1H, s, 11-OH), and 6.40 (1H, s, 14-H). Found: C, 73.49; H, 8.38%. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19%.

b): A solution of a mixture of **3b** and **4b** (ca. 1:1 ratio, 1.120 g) in pyridine (4.0 ml) was mesylated with methanesulfonyl chloride (0.23 ml) as described in a). The crude mesylates (1.295 g) were treated with sodium iodide (713 mg) in refluxing ethyl methyl ketone (25 ml) to give a mixture of iodides (1.286 g). This was further refluxed with aqueous sodium hydroxide (20%, 3.2 ml) in methanol (16 ml) for 1 h. The crude product was chromatographed on silica gel (25 g), using hexane–benzene (3:7) as an eluent, to give **5b** (520 mg, 60.7% yield), mp 167.5—169 °C (from hexane), $[\alpha]_D$+33.0 ° (c 0.58), IR 3560, 3375, and 1718 cm^{-1}; ^{1}H NMR δ=1.25 and 1.32 (each 3H and s, 4-CH_3 and 10-CH_3), 1.27 (3H, d, J=7 Hz, 15-CH_3), 3.66 (3H, s, $-CO_2CH_3$), 4.04 (1H, dd, J=8 and 7 Hz) and 4.68 (1H, t, J=8 Hz) (15-CH_2O–), 4.87 (1H, s, 11-OH), and 6.42 (1H, s, 14-H). Found: C, 73.04; H, 8.45%. Calcd for $C_{21}H_{28}O_4$: C, 73.22; H, 8.19%.

(15*S*)-12,16-Epoxy-8,11,13-abietatriene-11,18-diol (6a) and Its (15*R*)-Epimer (6b). a): A mixture of **5a** (794 mg) and lithium aluminum hydride (149 mg) in dry ether (7.0 ml) was stirred at room temperature for 1 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 to give a crude **6a** (740 mg). This was recrystallized from acetone–hexane, mp 159—160.5 °C, $[\alpha]_D$+78.9 ° (*c* 1.47), IR 3630, 3565, and 3450 cm^{-1}; ^1H NMR (60 MHz) δ=0.89 (3H, s, 4-CH_3), 1.27 (3H, d, *J*=7 Hz, 15-CH_3), 1.39 (3H, s, 10-CH_3), 3.16 (1H, d, *J*=11 Hz) and 3.50 (1H, d, *J*=11 Hz) (-$C\underline{H}_2OH$), 4.01 (1H, t, *J*=8 Hz) and 4.67 (1H, t, *J*=8 Hz) (15-CH_2O-), 5.12 (1H, bs, 11-OH), and 6.40 (1H, s, 14-H). Found: C, 75.92; H, 9.21%. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92%.

b): A mixture of **5b** (1.006 g) and lithium aluminum hydride (189 mg) in dry ether (15 ml) was stirred at room temperature for 1 h. The mixture was treated as described in a) to give a crude **6b** (1.001 g). This was recrystallized from acetone–hexane, mp 183.5—185.5 °C, $[\alpha]_D$+66.7 ° (*c* 2.03), IR 3625, 3565, and 3450 cm^{-1}; ^1H NMR (60 MHz) δ=0.88 (3H, s, 4-CH_3), 1.28 (3H, d, *J*=7 Hz, 15-CH_3), 1.39 (3H, s, 10-CH_3), 3.16 (1H, d, *J*=10 Hz) and 3.50 (1H, d, *J*=10 Hz) (-$C\underline{H}_2OH$), 4.04 (1H, t, *J*=8 Hz) and 4.65 (1H, t, *J*=8 Hz) (15-CH_2O-), 5.20 (1H, s, 11-OH), and 6.43 (1H, s, 14-H). Found: C, 76.08; H, 9.14%. Calcd for $C_{20}H_{28}O_3$: C, 75.91; H, 8.92%.

(15*S*)-12,16-Epoxy-8,11,13-abietatrien-11-ol (8a) and Its (15*R*)-Epimer (8b). a): A mixture of the crude **6a** (730 mg) and methanesulfonyl chloride (0.26 ml) in pyridine (7.0 ml) was stirred at 0—5 °C for 30 min and then at room temperature for 2.5 h. The mixture was 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 to give a crude mesylate (**7a**) (1.025 g), ^1H NMR (60 MHz) δ=0.98 (3H, s, 4-CH_3), 1.30 (3H, d, *J*=7 Hz, 15-CH_3), 1.40 (3H, s, 10-CH_3), 3.01 (3H, s, -$CH_2OSO_2C\underline{H}_3$), 3.75 (1H, d, *J*=9 Hz) and 4.10 (1H, d, *J*=9 Hz) (-$C\underline{H}_2OMs$), 4.02 (1H, t, *J*=8 Hz) and 4.67 (1H, t, *J*=8 Hz) (15-CH_2O-), and 6.42 (1H, s, 14-H).

A stirred mixture of the above crude **7a** (1.010 g), sodium iodide (1.95 g), and zinc powder (1.68 g) in *N*,*N*-dimethylformamide (24 ml) was heated at 120—125 °C for 10 h. The mixture was cooled, diluted with ether, and then filtered. The filtrate was washed successively with aqueous sodium thiosulfate and brine, dried, and evaporated in vacuo. The residue was chromatographed on silica gel (30 g), using hexane–benzene (3:2) as an eluent, to give **8a** (389 mg: 56.2% yield from **5a**). IR 3575 cm^{-1}, $[\alpha]_D$+76.3 ° (*c* 0.93); ^1H NMR (60 MHz) δ=0.95 (6H, s, -$\underset{|}{C}(CH_3)_2$), 1.28 (3H, d, *J*=7 Hz, 15-CH_3), 1.35 (3H, s, 10-CH_3), 4.01 (1H, t, *J*=8.5 Hz) and 4.65 (1H, t, *J*=8.5 Hz) (15-CH_2O-), 4.91 (1H, s, 11-OH), and 6.40 (1H, s, 14-H). Found: C, 79.75; H, 9.58%. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39%.

b): A solution of the crude **6b** (1.050 g) in pyridine (10 ml) was treated with methanesulfonyl chloride (0.37 ml) as described in a) to give a crude mesylate (**7b**) (1.239 g). ^1H NMR (60 MHz) δ=0.99 (3H, s, 4-CH_3), 1.29 (3H, d, *J*=7 Hz, 15-CH_3), 1.38 (3H, s, 10-CH_3), 3.01 (3H, s, -$CH_2OSO_2C\underline{H}_3$), 3.72 (1H, d, *J*=9 Hz) and 4.08 (1H, d, *J*=9Hz) (-$C\underline{H}_2OMs$), 4.03 (1H, dd, *J*=9 and 6 Hz) and 4.68 (1H, t, *J*=9 Hz) (15-CH_2O-), 5.02 (1H, s, 11-OH), and 6.42 (1H, s, 14-H).

A stirred mixture of the above crude **7b** (1.239 g), sodium iodide (2.36 g), and zinc powder (2.05 g) in *N*,*N*-dimethylformamide (20 ml) was heated at 120—125 °C for 10 h. After the work-up as described in a), the crude product was chromatographed on silica gel (30 g), using hexane–benzene (3:2) as an eluent, to give **8b** (469 mg: 53.4% yield from **5b**). IR 3565 cm^{-1}; ^1H NMR (60 MHz) δ=0.93 (6H, s, -$\underset{|}{C}(CH_3)_2$), 1.27 (3H, d, *J*=7 Hz, 15-CH_3), 1.33 (3H, s, 10-CH_3), 4.00 (1H, dd, *J*=8 and 7 Hz) and 4.63 (1H, t, *J*=8 Hz) (15-CH_2O-), 4.96 (1H, s, 11-OH), and 6.40 (1H, s, 14-H). Found: C, 79.82; H, 9.63%. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39%.

(15*S*)-12,16-Epoxy-8,12-abietadiene-11,14-dione (9a) and Its (15*R*)-Epimer (9b). a): A stirred solution of **8a** (33.2 mg) in *N*,*N*-dimethylformamide (4.0 ml) was protected from light with aluminum foil. After the addition of a solution of Fremy's salt (potassium nitrosodisulfonate) (149 mg) and potassium dihydrogenphosphate (58 mg) in water (6.0 ml), the mixture was stirred at room temperature under a stream of nitrogen for 2 h. The mixture was then 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 hexane–chloroform (1:1) as an eluent, to give recovered **8a** (3.8 mg: 11.4% yield). Further elution afforded **9a** (28.0 mg: 80.2% yield), mp 143.5—144.5 °C (from methanol), $[\alpha]_D$+11.6 ° (*c* 1.73), IR 1670, 1650, and 1640 cm^{-1}; ^1H NMR δ=0.88 and 0.91 (each 3H and s, -$\underset{|}{C}(CH_3)_2$), 1.25 (3H, s, 10-CH_3), 1.28 (3H, d, *J*=7 Hz, 15-CH_3), 3.50 (1H, m, 15-H), and 4.18 (1H, dd, *J*=9 and 6 Hz) and 4.71 (1H, t, *J*=9 Hz) (15-CH_2O-). Found: C, 76.08; H, 8.52%. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34%.

b): A stirred solution of **8b**(180.0 mg) in *N*,*N*-dimethylformamide (21.6 ml) was protected from light with aluminum foil. After the addition of a solution of Fremy's salt (804 mg) and potassium dihydrogenphosphate (310 mg) in water (32.4 ml), the mixture was stirred at room temperature under a stream of nitrogen for 2 h. After the work-up as described in a), the crude product was chromatographed on silica gel (15 g), using hexane–chloroform (1:1) as an eluent, to give recovered **8b** (14.9 mg: 8.3% yield) and **9b** (155.7 mg: 82.6% yield), mp 154—155 °C (from methanol), $[\alpha]_D$+128 ° (*c* 0.85), IR 1670, 1650, and 1640 cm^{-1}; ^1H NMR δ=0.89 and 0.92 (each 3H and s, -$\underset{|}{C}(CH_3)_2$), 1.25 (3H, s, 10-CH_3), 1.30 (3H, d, *J*=7 Hz, 15-CH_3), 3.50 (1H, m, 15-H), and 4.18 (1H, dd, *J*=9 and 6 Hz) and 4.72 (1H, t, *J*=9 Hz) (15-CH_2O-). Found: C, 76.33; H, 8.54%. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34%.

(15*S*)-11,14-Diacetoxy-12,16-epoxy-8,11,13-abietatriene (10a) and Its (15*R*)-Epimer (10b). a): A mixture of **9a** (73.4 mg), acetic anhydride (0.5 ml), and zinc powder (50 mg) in pyridine (1.0 ml) was stirred at 0—5 °C for 10 min and then at room temperature for 2.5 h. The mixture was poured into ice-dilute hydrochloric acid and extracted with ether. The ether extract was washed successively with aqueous sodium hydrogencarbonate and brine, dried, and evaporated in vacuo. The residue was chromatographed on silica gel (10 g), using ether–benzene (1:99) as an eluent, to give **10a** (88.0 mg: 94.1% yield), mp 161—162 °C (from hexane), $[\alpha]_D$+47.2 ° (*c* 1.63), IR 1758 cm^{-1}; ^1H NMR δ=0.88 and 0.91 (each 3H and s, -$\underset{|}{C}(CH_3)_2$), 1.23 (3H, s, 10-CH_3), 1.23 (3H, d, *J*=7 Hz, 15-CH_3), 2.27 (6H, s, 2-$OCOCH_3$), 3.52 (1H, m, 15-H), and 4.08 (1H, dd, *J*=9 and 6 Hz) and 4.63 (1H, t, *J*=9 Hz)

(15-CH_2O-). Found: C, 72.20; H, 8.26%. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05%.

b): A mixture of **9b** (53.0 mg), acetic anhydride (0.3 ml), and zinc powder (30 mg) in pyridine (0.5 ml) was stirred at 0—5 °C for 10 min and then at room temperature for 2.5 h. After the work-up as described in a), the crude product was recrystallized from hexane to give **10b** (48.2 mg: 71.4% yield), mp 168—170 °C, $[\alpha]_D$+87.5 ° (*c* 0.96), IR 1760 cm^{-1}; ^1H NMR δ=0.89 and 0.91 (each 3H and s, $-C(CH_3)_2$), 1.20 (3H, d, *J*=7 Hz, 15-CH_3), 1.23 (3H, s, 10-CH_3), 2.27 (6H, s, 2-$OCOCH_3$), 3.51 (1H, m, 15-H), and 4.08 (1H, dd, *J*=9 and 6 Hz) and 4.62 (1H, t, *J*=9 Hz) (15-CH_2O-). Found: C, 72.08; H, 8.17%. Calcd for $C_{24}H_{32}O_5$: C, 71.97; H, 8.05%. The mother liquor of recrystallization was evaporated in vacuo. The residue was chromatographed on silica gel (5 g), using ether–benzene (1:99) as an eluent, to give additional **10b** (16.5 mg: 24.4% yield).

(15*S*)-11,14-Diacetoxy-12,16-epoxy-8,11,13-abietatrien-7-one (11a) and Its (15*R*)-Epimer (11b). a): A mixture of **10a** (72.3 mg) and chromium trioxide (54.1 mg) in acetic acid (0.7 ml) was stirred at 0—5 °C for 5 min and then at room temperature for 1 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, and evaporated in vacuo. The residue was chromatographed on silica gel (10 g), using ether–benzene (1:99) as an eluent, to give **11a** (53.8 mg: 71.9% yield), $[\alpha]_D$+63.2 ° (*c* 0.87) (natural hyptol diacetate, $[\alpha]_D$+63.8 ° (*c* 0.24)[3]), IR 1765 and 1670 cm^{-1}; ^1H NMR δ=0.92 and 0.94 (each 3H and s, $-C(CH_3)_2$), 1.32 (3H, d, *J*=7 Hz, 15-CH_3), 1.33 (3H, s, 10-CH_3), 2.30 and 2.36 (each 3H and s, 2-$OCOCH_3$), 3.60 (1H, m, 15-H), and 4.19 (1H, dd, *J*=9 and 6 Hz) and 4.73 (1H, t, *J*=9 Hz) (15-CH_2O-). Found: C, 69.77; H, 7.48%. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30%.

b): A mixture of **10b** (120.1 mg) and chromium trioxide (90 mg) in acetic acid (1.2 ml) was stirred at 0—5 °C for 5 min and then at room temperature for 1 h. After the work-up as described in a), the crude product was chromatographed on silica gel (10 g), using ehter-benzene (5:95) as an eluent, to give **11b** (91.9 mg: 72.4% yield), mp 178—179 °C (from hexane), $[\alpha]_D$+119 ° (*c* 2.39), IR 1765 and 1670 cm^{-1}; ^1H NMR δ=0.91 and 0.94 (each 3H and s, $-C(CH_3)_2$), 1.27 (3H, d, *J*=6 Hz, 15-CH_3), 1.30 (3H, s, 10-CH_3), 2.29 and 2.35 (each 3H and s, 2-$OCOCH_3$), 3.57 (1H, m, 15-H), and 4.21 (1H, dd, *J*=9 and 6 Hz) and 4.72 (1H, t, *J*=9 Hz) (15-CH_2O-). Found: C, 69.50; H, 7.40%. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30%.

(15*S*)-12,16-Epoxy-11,14-dihydroxy-8,11,13-abietatrien-7-one (Hyptol) (1a) and Its (15*R*)-Epimer (1b). a): A mixture of **11a** (19.1 mg) and dilute hydrochloric acid (15%, 0.2 ml) in ethanol (1.0 ml) was refluxed for 24 h. After removal of the ethanol in vacuo, the residue was 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 hexane–chloroform (1:2) as an eluent, to give **1a** (14.9 mg: 98.0% yield), mp 200—203 °C (from hexane), $[\alpha]_D$+52.5 ° (*c* 0.20), IR 3570, 3325, and 1620 cm^{-1}; ^1H NMR δ=0.95 (6H, s, $-C(CH_3)_2$), 1.36 (3H, s, 10-CH_3), 1.39 (3H, d, *J*=7 Hz, 15-CH_3), 3.68 (1H, m, 15-H), 4.26 (1H, dd, *J*=9 and 6 Hz) and 4.77 (1H, t, *J*=9 Hz) (15-CH_2O-), 4.63 (1H, s, 11-OH), and 13.39 (1H, s, 14-OH). Found: C, 72.81; H, 7.76%. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93%. The physical and spectral data of the synthetic **1a** were identical to those of natural hyptol, mp 202—203 °C,[1] $[\alpha]_D$+56 °;[1] ^1H NMR[3] δ=0.95 (6H, s, $-C(CH_3)_2$), 1.36 (3H, s, 10-CH_3), 1.39 (3H, d, *J*=7 Hz, 15-CH_3), 3.68 (1H, m, 15-H), 4.26 (1H, dd, *J*=9 and 6 Hz) and 4.77 (1H, t, *J*=9 Hz) (15-CH_2O-), 4.62 (1H, s, 11-OH), and 13.39 (1H, s, 14-OH).

b): A mixture of **11b** (52.6 mg) and dilute hydrochloric acid (15%, 0.3 ml) in ethanol (2.0 ml) was refluxed for 23 h. After the work-up as described in a), the crude product was chromatographed on silica gel (5 g), using hexane–chloroform (1:2) as an eluent, to give **1b** (30.0 mg: 71.6% yield), mp 210—211 °C (from hexane), $[\alpha]_D$+127 ° (*c* 0.46), IR 3575, 3350, and 1620 cm^{-1}; ^1H NMR δ=0.95 (6H, s, $-C(CH_3)_2$), 1.34 (3H, s, 10-CH_3), 1.38 (3H, d, *J*=6 Hz, 15-CH_3), 3.70 (1H, m, 15-H), 4.25 (1H, dd, *J*=9 and 6 Hz) and 4.79 (1H, t, *J*=9 Hz) (15-CH_2O-), 4.63 (1H, s, 11-OH), and 13.39 (1H, s, 14-OH). Found: C, 72.57; H, 8.14%. Calcd for $C_{20}H_{26}O_4$: C, 72.70; H, 7.93%.

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