# Absolute Stereochemistry of Salvic Acid and Related Diterpenes

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# ABSOLUTE STEREOCHEMISTRY OF SALVIC ACID AND RELATED DITERPENES

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ABSTRACT.—The stereochemistry of salvic acid [**1**] and related diterpenes has been established on the basis of their chemical transformation into methyl dihydroeperuate.

The labdane diterpenes are some of the most common types of diterpenes from higher plants. Salvic acid and derivatives have been found in the tribe Eupatorieae (Compositae). Spectroscopy ($^1$H nmr, cd/ord, uv) has been generally applied to determine the stereochemistry of this class of diterpenes, but these methods have their limitations and conclusions drawn from them should be treated with reservations (1).

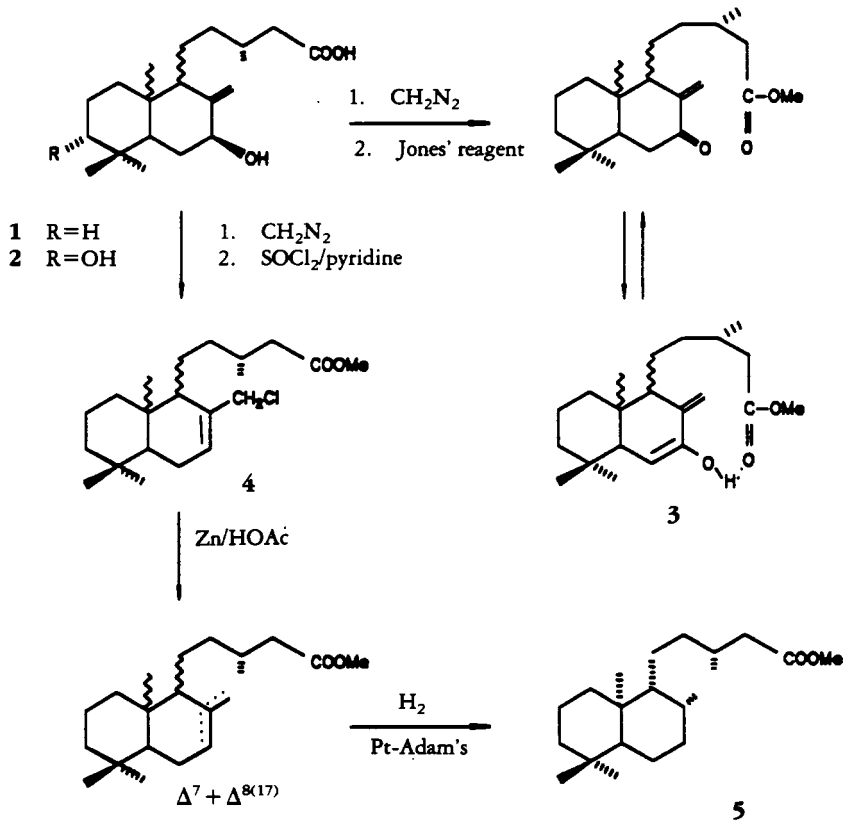
In an earlier paper (2) we reported the isolation of salvic acid [**1**] and its diol **2** and their structural determination by spectral and chemical techniques. The problem was that the absolute stereochemistry proposed in the literature for salvic acid (3) was the opposite of that exhibited by the diol **2** when reduced with $LiAlH_4$ and compared with 8(17)-labdene-3β,7α,15-triol isolated from *Halimium viscosum* (4). Diol **2** belongs to the eperuic acid optical series, while salvic acid has up to now been assigned to that of labdanolic acid. Although both series have occurred in the same plant (5), this is unlikely in this case. This paper reports the establishment of the absolute configuration of salvic acid [**1**] by chemical means by conversion to methyl dihydroeperuate **5**, a compound with known absolute stereochemistry (5).

The starting material was salvic acid [**1**] which was to be treated with $CH_2N_2$ followed by oxidation with Jones' reagent, giving the appropriate ketone which would then be reduced by the Huang-Minlon process. This sequence of reactions did not occur. An enol in equilibrium with the ketone **3** was probably obtained, as shown in the $^1$H-nmr spectrum in which a sharp peak at δ 9.35 (s, 1H) appeared, assigned to a chelated hydroxyl (Scheme 1).

This unwanted result led to a change in strategy. Compound **1** was treated with $CH_2N_2$ to give the appropriate methyl ester which was then treated with thionyl chloride in pyridine, affording **4** in good yield. The $^1$H-nmr spectrum shows a triplet at δ 5.86 for a vinylic hydrogen, a pair of doublets at δ 4.13 and 3.96 attributed to a $-CH_2Cl$ group, and a singlet at δ 3.95 typical of a methyl ester. In the methyl region, three singlets are visible (2 × C-4, C-10) and a doublet corresponding to C-13. When **4** was treated with zinc dust and HOAc under reflux, it gave a mixture of hydrocarbons at $\Delta^7$ and $\Delta^{8(17)}$ as can be seen from the $^1$H-nmr spectrum where three singlets appear at δ 3.85, 4.87, and 4.44, corresponding to the vinyl protons of the $\Delta^7$ and $\Delta^{8(17)}$ isomers and a new methyl at C-8, respectively. The above mixture was not purified and was hydrogenated with Adam's catalyst in EtOAc to afford a product with the physical and spectral properties of methyl dihydroeperuate [**5**] (see Experimental). This direct transformation of **1** to **5** establishes the configuration of the diterpenes from *Eupatorium salvia* (2), which have α-oriented C-9–C-11 and C-10–C-18 bonds as is customary in diterpenes of the eperuic acid optical series.

## EXPERIMENTAL

Mp's were determined on a Koefler hot-plate apparatus and are uncorrected. Rotations were




SCHEME 1.

determined in $CHCl_3$. Ir spectra were recorded on a Perkin-Elmer spectrometer, Model 257, nmr spectra on a Bruker Model WP-200 SY (200 MHz), using $CHCl_3$ as internal standard, and mass spectra on a VG Micromass ZAB-2F spectrometer. Merck Si gel (0.06–0.2 mm) was used for cc. Tlc was carried out with Schleicher und Schüll Si gel. Spots were revealed by spraying with "oleum" [$H_2SO_4$-$H_2O$-HOAc (4:16:80)] and heating to 100°. All solvents were dried and distilled immediately before use, and all the reactions were run under $N_2$ or Ar atmosphere.

METHYLATION OF **1**.—A solution of **1** (1.0 g) in $Et_2O$ was treated with gaseous $CH_2N_2$ generated from *N*-methyl-*N*-nitroso-*p*-toluene sulfonamide (15 g) dissolved in $Et_2O$ and gave salvic acid methyl ester (0.96 g): colorless oil; $[\alpha]_D$ +19° ($c$ = 2.5); $\nu$ max (film) 3453, 3180, 2980, 1740, 1645, 1460, 900 $cm^{-1}$; $^1H$ nmr (200 MHz, $CDCl_3$) δ 5.03 (s, 1H, H-17), 4.61 (s, 1H, H-17), 4.36 (s, 1H, H-7), 3.65 (s, 3H, OMe), 0.96 (d, 3H, $J$ = 6.4 Hz, Me-16), 0.85 (s, 3H, Me-18), 0.79 (s, 3H, Me-19), 0.64 (s, 3H, Me-20).

This ester (0.5 g) was dissolved in $Me_2CO$ (10 ml) which had previously been distilled over $KMnO_4$. Jones' reagent was added with vigorous shaking until the color of the reagent persisted. The reaction mixture was shaken for 2 h at room temperature, after which drops of MeOH were added slowly and the mixture was diluted with $H_2O$. The $Me_2CO$ was evaporated off and the mixture extracted with $Et_2O$; it was washed with $Na_2CO_3$ and $H_2O$. After evaporating off the solvent, 0.4 g of reaction product was obtained. Cc over Si gel [*n*-hexane–Be (7:3)] yielded an enol (0.2 g) in equilibrium with the ketone **3**: colorless oil; $[\alpha]_D$ 0° ($c$ = 1.0); $\nu$ max (film) 2970, 1740, 1730, 1470, 1300, 1070 $cm^{-1}$; $^1H$ nmr (200 MHz, $CDCl_3$) δ 9.35 (s, 1H, OH), 5.80 (s, 1H, H-17), 5.06 (s, 1H, H-17), 3.64 (s, 3H, OMe), 0.95 (d, 3H, $J$ = 6.3 Hz, Me-16), 0.84 (s, 3H, Me-18), 0.76 (s, 3H, Me-19), 0.64 (s, 3H, Me-20); *m/z* $[M]^+$ 334 (63), 303 (22), 293 (18), 261 (26), 233 (47), 220 (69), 165 (27), 123 (100), 109 (75).

HALOGENATION OF SALVIC ACID METHYL ESTER.—The methyl ester (0.4 g) was dissolved in pyridine (40 ml), and $SOCl_2$ (0.5 g) was added. The mixture was stirred at −5° under $N_2$ for 2 h, and the usual workup gave a colorless oil **4** (95% yield): $^1H$ nmr (200 MHz, $CDCl_3$) δ 5.86 (de-

formed t, 1H, H-7), 4.13 (d, 1H, $J = 11.0$ Hz, H-17), 3.96 (d, 1H, $J = 11.0$ Hz, H-17), 3.64 (s, 3H, OMe), 0.95 (d, 3H, $J = 6.4$ Hz, Me-16), 0.85 (s, 3H, Me-18), 0.83 (s, 3H, Me-19), 0.72 (s, 3H, Me-20); *m/z* $[M]^+$ 355 (2), $[M - HCl]^+$ 318 (100), 217 (12), 194 (20), 189 (20).

REDUCTION OF **4**.—Compound **4** (0.35 g) was treated with HOAc (30 ml) and zinc dust (2 g) under reflux for 1 h. Usual workup yielded a mixture of $\Delta^7$ and $\Delta^{8(17)}$ hydrocarbons in 80% yield: colorless oil; $^1$H nmr (200 MHz, $CDCl_3$) δ 5.35 (br s, 1H, H-7), 4.78 (s, 1H, H-17), 4.44 (s, 1H, H-17), 3.59 (s, 6H, 2 × OMe), 1.62 (s, 3H, Me-17), 0.93–0.64 (br s, 24H, 8 × OMe); *m/z* $[M]^+$ 320 (34), $[M - Me]^+$ 305 (58), 289 (6), 271 (7), 264 (6), 249 (5).

HYDROGENATION OF $\Delta^7$ AND $\Delta^{8(17)}$ HYDROCARBONS.—The hydrocarbon mixture (130 mg) was hydrogenated in EtOAc (25 ml) in the presence of $PtO_2$ (40 mg). When no more hydrogen was being absorbed, the reaction mixture was filtered and the solvent evaporated, and a single product was obtained and identified as methyl dihydroeperuate [**5**] (120 mg): colorless oil; $[\alpha]_D - 19°$ ($c = 5.8$) [lit. (5) $[\alpha]_D - 22°$].

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