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SYNTHESIS OF TAXOQUINONE, 7α-ACETOXYROYLEANONE, DEHYDROROYLEANONE, HORMINONE, 7-OXOROYLEANONE, AND INUROYLEANOL

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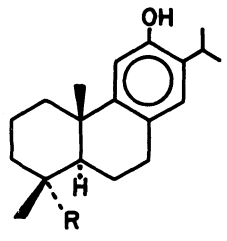
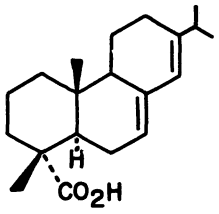
Oxidation of ferruginol (II) with benzoyl peroxide gave 12-benzoyloxy-11-hydroxyabieta-8,11,13-triene (X) which was converted into taxoquinone (IV), 7α-acetoxyroyleanone (V), dehydroroyleanone (VI), horminone (VII), 7-oxoroyleanone (VIII), and inuroyleanol (IX).

In our previous communication,[1] it has been reported on the successful oxidation of C-11 position in methyl 12-hydroxyabieta-8,11,13-trien-18-oate (I)[2] with benzoyl peroxide. As an extension of the work, we further attempted the conversion of ferruginol (II) prepared[3] from (-)-abietic acid (III) via I, into naturally-occurring tricyclic diterpenes possessing an oxygen-function at C-11 position. Since (-)-abietic acid has been synthesized, any conversion starting from II can be regarded as a formal total synthesis. This communication[4] will describe the synthesis of taxoquinone (IV),[5,6] 7α-acetoxyroyleanone (V),[7,8] dehydroroyleanone (VI),[5,7,9,10]



I R=CO_2Me
II R=Me



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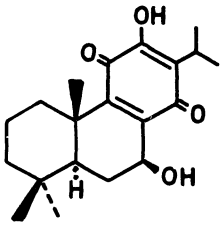
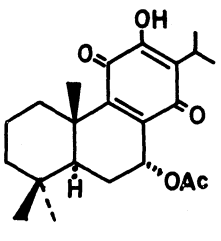


IV



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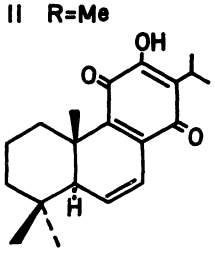

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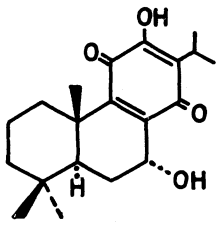
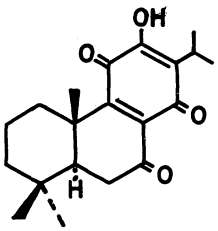
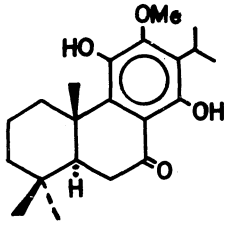


VII



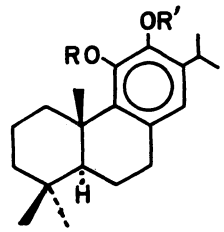
VIII



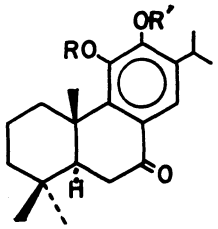
IX

horminone (VII),[5,11] 7-oxoroyleanone (VIII),[5,8] and inuroyleanol (IX).[8]

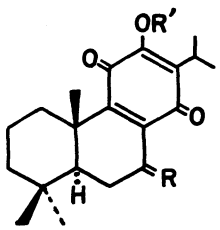
Oxidation[3] of II with benzoyl peroxide in chloroform (r.t., 4 hr) afforded 12-benzoyloxy-11-hydroxyabieta-8,11,13-triene (X: 44%) which gave a positive Gibb's test,[12] suggesting the presence of an aromatic proton para to a phenolic hydroxyl group; mp 132.5-133°C, $[\alpha]_D$ +81.2°, IR: 3575, 3350, 1740 cm^{-1}, NMR: 0.97 (s, $-\overset{|}{C}(CH_3)_2$), 1.17 and 1.19 (each d and J=7 Hz, $-CH(\underline{CH}_3)_2$), 1.33 (s, C_{10}-CH_3), 5.17 (s, -OH), 6.50 (s, C_{14}-H), 7.4-8.3 (m, $-C_6H_5$). Methylation of X in refluxing methyl ethyl ketone with methyl iodide in the presence of potassium carbonate (8 hr) afforded two monomethyl ethers, XI (38%, mp 183.5-184.5°C) and XII (60%, mp 125-126°C). Reductive cleavage of benzoyl group in XI was carried out with lithium aluminum hydride in refluxing ether (2 hr) and the resulting phenol (XIII, 80%, mp 94-94.5°C) showed a positive Gibb's test. Oxidation of XI with chromic anhydride in acetic acid (r.t., 22 hr) gave a 7-oxo compound (XIV, 54%), mp 197-198°C, $[\alpha]_D$ +68.9°, IR: 1739, 1676 cm^{-1}, which on alkaline hydrolysis gave cryptojaponol (XV, mp 205-206.5°C).[13] Thus, the structure of XI was assigned as 11-benzoyloxy-12-methoxyabieta-8,11,13-triene. Subsequently, XII was hydrolyzed with aqueous sodium hydroxide in refluxing methanol (1 hr) to give the corresponding phenol (XVI, 80%, mp 114.5-115°C) which, in contrast with XIII, gave a negative Gibb's test. XII was also subjected to oxidation with chromic anhydride in acetic acid (r.t., 24 hr) to give a benzoyloxy p-benzoquinone (XVII, 27%, mp 196-197°C) which on alkaline hydrolysis gave royleanone (XVIII, mp 181.5-183°C),[7] and a 7-oxo compound (XIX, 44%), mp 163-163.5°C, $[\alpha]_D$ +38°, IR: 1740, 1678 cm^{-1}, NMR: 0.99 (s, $-\overset{|}{C}(CH_3)_2$), 1.22 and 1.27 (each d and J=7 Hz, $-CH(\underline{CH}_3)_2$), 1.40 (s, C_{10}-CH_3), 3.70 (s, $-OCH_3$), 7.3-8.4 (m, $-C_6H_5$), 7.76 (s, C_{14}-H). The above results suggested the structure of XII to be 12-benzoyloxy-11-methoxyabieta-8,11,13-triene. Reduction of XIX with sodium borohydride in methanol (0°C, 3 hr) followed by acetylation of the resulting alcoholic product with acetic anhydride in pyridine (r.t., 22 hr) gave a mixture of 7β-acetoxy-12-benzoyloxy-11-methoxyabieta-8,11,13-triene (XX, 75%) and its 7α-acetoxy isomer (XXI, 15%), mp 176-177°C, $[\alpha]_D$ +75.2°. The stereochemistry of the acetoxyl groups was established on the basis of the presence of C-7 proton signals with half-height width of 12 Hz at δ 5.90 for XX and 5 Hz at δ 5.86 ppm for XXI in their NMR spectra. This reaction procedure leading to the 7-acetoxy compounds is suitable for the synthesis of taxoquinone (IV) possessing a 7β-hydroxyl group. However, in order to obtain 7α-acetoxyroyleanone (V) and horminone (VII) it is necessary to prepare XXI predominantly. For this purpose, the



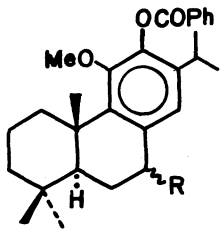
X R=H, R'=COPh
XI R=COPh, R'=Me
XII R=Me, R'=COPh
XIII R=H, R'=Me
XVI R=Me, R'=H



XIV R=COPh, R'=Me
XV R=H, R'=Me
XIX R=Me, R'=COPh



XVII R=H_2, R'=COPh
XVIII R=H_2, R'=H
XXII R=α-H, β-OAc, R'=COPh
XXIII R=α-H, β-OH, R'=Me
XXIV R=α-OAc, β-H, R'=COPh
XXV R=O, R'=Me



XX R=β-OAc
XXI R=α-OAc

direct acetoxylation on C-7 position in XII was attempted and the ratio of XX and XXI could be improved by treatment with lead tetraacetate in refluxing acetic acid (N_2 atmosphere, 40 min) in 57% yield (ca. 1:2 ratio). Oxidation of XX in acetic acid with chromic anhydride (r.t., 24 hr) afforded 7β-acetoxy-12-benzoyloxy-11,14-dioxoabieta-8, 12-diene (XXII, 37%), mp 155-160°C, $[\alpha]_D$ +30°, IR: 1737, 1663 cm^{-1}. Hydrolysis of XXII with aqueous sodium hydroxide in methanol (reflux, 30 min) followed by treatment with dilute hydrochloric acid (reflux, 5 min) gave taxoquinone (IV, 68%),[14] mp 206-207°C, $[\alpha]_D$ +344°, IR: 3548, 3378, 1671, 1647, 1623, 1597 cm^{-1}, NMR ($CDCl_3$): 0.93 (s, $-\dot{C}(CH_3)_2$), 1.22 (d, J=7 Hz, $-CH(\underline{C}H_3)_2$), 1.35 (s, C_{10}-CH_3), 3.84 (d, J=2 Hz, C_7-OH), 4.84 (m, $W_{1/2}$=20 Hz, C_7-H), 7.33 (s, C_{12}-OH), Mass: m/e 332 (M^+). According to the methods of Eugster et al.,[5] the product IV was converted into its methyl ether (XXIII), dehydroroyleanone (VI),[14] mp 166-167°C, $[\alpha]_D$ -609°, IR: 3363, 1665, 1635, 1610 cm^{-1}, NMR ($CDCl_3$): 0.98, 1.02, and 1.04 (each s, $-\dot{C}(CH_3)_2$ and C_{10}-CH_3), 1.22 (d, J=7 Hz, $-CH(\underline{C}H_3)_2$), 2.14 (t, J=3 Hz, C_5-H), 6.45 (dd, J=3 and 10 Hz, C_6-H), 6.81 (dd, J=3 and 10 Hz, C_7-H), 7.32 (s, C_{12}-OH), and 7-oxoroyleanone (VIII),[15] mp 202-203°C, IR: 3400, 1695, 1663, 1645, 1575 cm^{-1}, NMR ($CDCl_3$): 0.93 and 0.96 (each s, $-\dot{C}(CH_3)_2$), 1.22 (d, J=7 Hz, $-CH(\underline{C}H_3)_2$), 1.36 (s, C_{10}-CH_3), 6.98 (s, -OH). Similarly, XXI was also oxidized with chromic anhydride in acetic acid (r.t., 20 hr) to afford 7α-acetoxy-12-benzoyloxy-11,14-dioxoabieta-8,12-diene (XXIV, 23%), mp 261-262°C, $[\alpha]_D$ +42°, IR: 1738, 1664 cm^{-1}. This was then subjected to partial hydrolysis with sodium hydrogencarbonate in refluxing aqueous methanol (1 hr) to give 7α-acetoxyroyleanone (V, 97%),[14] mp 212-214°C, $[\alpha]_D$ -7°, IR: 3390, 1736, 1671, 1642, 1608 cm^{-1}, NMR ($CDCl_3$): 0.89 (s, $-\dot{C}(CH_3)_2$), 1.19 and 1.22 (each d and J=7 Hz, $-CH(\underline{C}H_3)_2$), 1.24 (s, C_{10}-CH_3), 2.02 (s, $-OCOCH_3$), 5.94 (m, $W_{1/2}$=6 Hz, C_7-H), 7.13 (s, C_{12}-OH). Alkaline hydrolysis of XXIV followed by treatment with dilute hydrochloric acid afforded horminone (VII, 81%),[14] mp 176-178°C, $[\alpha]_D$ -120°,

IR: 3570, 3380, 1671, 1647, 1627, 1601 cm^{-1}, NMR ($CDCl_3$): 0.91 and 0.99 (each s, $-\dot{C}(CH_3)_2$), 1.22 (s, C_{10}-CH_3), 1.22 (d, J=7 Hz, $-CH(\underline{CH_3})_2$), 3.05 (s, C_7-OH), 4.75 (m, $W_{1/2}$=9 Hz, C_7-H), 7.27 (s, C_{12}-OH). Finally, XXIII was oxidized with chromic anhydride-pyridine complex (r.t., 48 hr) to give the corresponding 7-oxo compound (XXV, 22%),[8] mp 90-92°C, which on reduction with sodium sulfite in acetic acid (95°C, 2 min) gave inuroyleanol (IX, 70%),[15] mp 185-186°C, $[\alpha]_D$ +106°, IR: 3520, 1620 cm^{-1}, NMR ($CDCl_3$): 0.96 (s, $-C(CH_3)_2$), 1.37 (s, C_{10}-CH_3), 1.39 (d, J=7 Hz, $-CH(\underline{CH_3})_2$), 3.80 (s, $-OCH_3$), 5.72 (s, C_{11}-OH), 13.30 (s, C_{14}-OH).

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3) The details will be report elsewhere.
4) IR spectra were taken in $CHCl_3$ and NMR in CCl_4 unless otherwise specified. Their chemical shifts are presented in terms of δ values. Optical rotations were measured in $CHCl_3$ on a Yanaco OR-50D.
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14) The synthetic IV, V, VI, and VII were respectively shown to be identical with natural taxoquinone (mp 212-214°C, $[\alpha]_D$ +340°),[6] 7α-acetoxyroyleanone (mp 212-214.5°C, $[\alpha]_D$ -14°),[7] dehydroroyleanone (mp 166-168.5°C, $[\alpha]_D$ -620°),[7] and horminone (mp 178-180°C, $[\alpha]_D$ -130°)[11] by mixed mp and spectral comparisons (IR and NMR).
15) The IR and NMR spectra of the synthetic VIII and IX were identical with those published[8] for 7-oxoroyleanone (mp 204-205°C) and inuroyleanol (mp 185-187°C, $[\alpha]_D$ +113.9°), respectively.

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