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SYNTHESIS OF (±)-14-HYDROXY-12-ISOPROPYL-3-OXOPODOCARPA-1,8,11,13- AND (±)-14-HYDROXY-12-ISOPROPYL-1-OXOPODOCARPA-2,8,11,13-TETRAENES, AND (±)-12-HYDROXY-1-OXOTOTARA-2,8,11,13-TETRAENE

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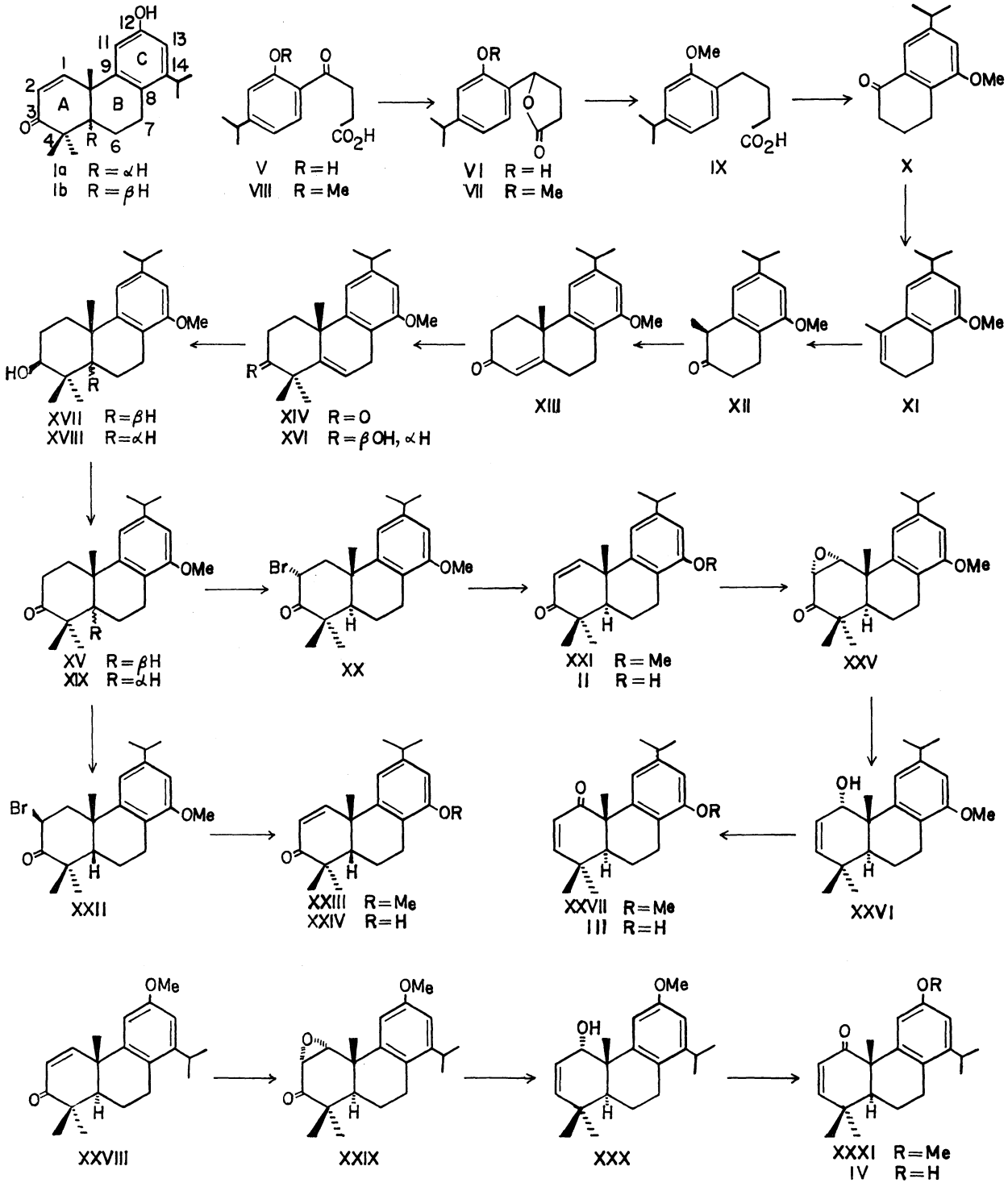
For structural elucidation of shonanol, (±)-14-hydroxy-12-isopropyl-3-oxopodocarpa-1,8,11,13-tetraene (II), (±)-14-hydroxy-12-isopropyl-1-oxopodocarpa-2,8,11,13-tetraene (III), and (±)-12-hydroxy-1-oxototara-2,8,11,13-tetraene (IV) were synthesized. However, the synthetic II-IV were shown to be not identical with shonanol.

Shonanol was isolated from Libocedrus formosana by Lin and Liu.[1] On the basis of spectral studies, its structure was tentatively deduced to be I, which is unique among tricyclic diterpenoids in containing an α,β-unsaturated keto group in ring A and a hydroxyl group at the position meta to the isopropyl group in ring C. In a previous communication,[2] the present authors reported the total synthesis of (±)-12-hydroxy-3-oxototara-1,8,11,13-tetraene (Ia) and its cis-isomer (Ib), and suggested that the structure of shonanol is not represented as Ia or Ib. Subsequently, we attempted the synthesis of some isomers of I to know their spectral and physical properties, and to compare them with natural shonanol. This communication[3] will describe the total synthesis of 14-hydroxy-12-isopropyl-3-oxopodocarpa-1,8,11,13-tetraene (II), 14-hydroxy-12-isopropyl-1-oxopodocarpa-2,8,11,13-tetraene (III), and 12-hydroxy-1-oxototara-2,8,11,13-tetraene (IV), and the non-identity of the synthetic II-IV with shonanol.

Reduction of β-(2-hydroxy-4-isopropylbenzoyl)propionic acid (V)[2] with sodium borohydride, followed by treatment of the resulting alcohol with dilute sulfuric acid gave a γ-lactone (VI, mp 110-111.5°C), which was then methylated with diazomethane to give the corresponding methyl ether (VII, IR: 1765 cm^{-1}). This was also prepared by a similar reduction of β-(4-isopropyl-2-methoxybenzoyl)propionic acid (VIII).[2] The lactone (VII) was hydrogenolyzed using palladium-charcoal to give an acid (IX). Treatment of IX in benzene with phosphorous pentachloride, followed by intramolecular cyclization of the resulting acid chloride with anhydrous stannic chloride, gave a 1-tetralone deriva-

tive (X, IR: 1670 cm^{-1}). The Grignard reaction of X with methylmagnesium iodide afforded the corresponding alcohol which by dehydration with dilute sulfuric acid gave a dihydronaphthalene derivative (XI). This was then converted to 7-isopropyl-5-methoxy-1-methyl-2-tetralone (XII, mp 70-73°C, IR: 1710 cm^{-1}) by oxidation with perbenzoic acid and subsequent treatment with dilute sulfuric acid. Construction of the A ring was achieved by condensation of XII with methyl vinyl ketone in the presence of sodium amide, and an α,β-unsaturated ketone (XIII, mp 100.5-102°C, IR: 1663 cm^{-1}) was thus obtained. Methylation of XIII with methyl iodide in the presence of potassium t-butoxide gave 12-isopropyl-14-methoxy-3-oxopodocarpa-5,8,11,13-tetraene (XIV). Catalytic hydrogenation of XIV over platinum oxide in acetic acid afforded a cis-A/B-ring isomer (XV); IR: 1700 cm^{-1}; NMR: 0.80, 1.11, and 1.23 (each s, C_4-($C\underline{H}_3$)$_2$ and C_{10}-$C\underline{H}_3$), 1.24 (d, J=7 Hz, -CH($C\underline{H}_3$)$_2$), 3.78 (s, -O$C\underline{H}_3$), 6.43 and 6.71 (each bs, C_{11}-$\underline{H}$ and C_{13}-$\underline{H}$); as a major product. To obtain the trans-isomer, XIV was reduced with lithium aluminum hydride to give an alcohol (XVI),[4] which by catalytic hydrogenation over palladium-charcoal in methanol at 60°C/50 atm. gave a mixture of dihydro derivatives (ca. 1:5 ratio). Since the NMR spectra of these minor (XVII) and major alcohol (XVIII) showed signals at δ 0.43, 1.00, 1.17 ppm and at δ 0.84, 1.03, 1.17 ppm, due to methyl groups at the C-4 and C-10 positions, the configurations of the A/B ring junction in XVII and XVIII were assigned as cis and trans respectively. The alcohols, XVII and XVIII, were oxidized with Jones' reagent to give respectively XV and 12-isopropyl-14-methoxy-3-oxopodocarpa-8,11,13-triene (XIX); mp 92.5-93°C; IR: 1700 cm^{-1}; NMR: 1.12, 1.28, and 1.30 (each s, C_4-($C\underline{H}_3$)$_2$ and C_{10}-$C\underline{H}_3$), 1.23 (d, J=7 Hz, -CH($C\underline{H}_3$)$_2$), 3.74 (s, -O$C\underline{H}_3$), 6.37 and 6.60 (each bs, C_{11}-$\underline{H}$ and C_{13}-$\underline{H}$). Bromination of XIX with cupric bromide gave a bromo derivative (XX); IR: 1720 cm^{-1}; NMR: 5.03 (dd, J=13 and 6 Hz, -C$\underline{H}$Br-); which was then dehydrobrominated with lithium carbonate and lithium chloride in dimethylformamide to give an α,β-unsaturated keto derivative (XXI), mp 119-120°C, IR: 1660 cm^{-1}. The methyl ether (XXI) was then demethylated with boron tribromide to give II, mp 155.5-156°C; IR: 3600, 3400, 1660 cm^{-1}; UV: λ_{max}^{EtOH} nm (ε): 225 (19,600), 279 (1,400); NMR: 1.18 and 1.21 (each s, C_4-($C\underline{H}_3$)$_2$), 1.20 (d, J= 7 Hz, -CH($C\underline{H}_3$)$_2$), 1.40 (s, C_{10}-$C\underline{H}_3$), 5.89 (s, -O$\underline{H}$), 5.94 and 7.55 (each d and J=10 Hz, -COC$\underline{H}$=C$\underline{H}$-), 6.40 and 6.48 (each s, C_{11}-$\underline{H}$ and C_{13}-$\underline{H}$). The spectral data of II were different from those of natural shonanol.[1] Similarly, XV was also brominated to give a bromide (XXII); IR: 1720 cm^{-1}; NMR: 4.80 (dd, J=13 and 4 Hz, -C$\underline{H}$Br-); which was then converted to the corresponding unsaturated compound (XXIII); IR: 1667 cm^{-1}; NMR: 0.74 and 1.19 (each s, C_4-($C\underline{H}_3$)$_2$), 1.22 (d, J=7 Hz, -CH($C\underline{H}_3$)$_2$), 1.42 (s, C_{10}-$C\underline{H}_3$), 3.76 (s, -O$C\underline{H}_3$), 5.81 and 7.07 (each

d and J=10 Hz, -COC<u>H</u>=C<u>H</u>-), 6.41 and 6.63 (each s, C_{11}-<u>H</u> and C_{13}-<u>H</u>). Although conversion of XXIII (insufficient for demethylation) to 14-hydroxy-12-isopropyl-3-oxo-5βH-podocarpa-1,8,11,13-tetraene (XXIV) was not carried out, the NMR spectrum of XXIII suggested that shonanol is not represented as XXIV. Finally, preparation of the 1-oxo



derivatives (III, IV) was also carried out as follows. Oxidation of XXI with alkaline hydrogen peroxide, followed by treatment of the resulting epoxide (XXV) with hydrazine hydrate[5] gave an alcohol (XXVI). This was then oxidized with Jones' reagent to give 12-isopropyl-14-methoxy-1-oxopodocarpa-2,8,11,13-tetraene (XXVII); mp 124.5-125°C; IR: 1673 cm^{-1}; NMR: 5.77 and 6.35 (each d and J=10 Hz, -COC<u>H</u>=C<u>H</u>-). Demethylation of XXVII with boron tribromide gave the phenol (III); mp 185.5-186°C; IR: 3600, 3375, 1670 cm^{-1}; UV: λ_{max}^{EtOH} nm (ε): 223 (16,700), 281 (2,200); NMR: 1.18 (s, C_4-(C<u>H</u>$_3$)$_2$), 1.24 (d, J=7 Hz, -CH(C<u>H</u>$_3$)$_2$), 1.58 (s, C_{10}-C<u>H</u>$_3$), 2.87 (m, -C<u>H</u>(CH$_3$)$_2$), 5.34 (bs, -O<u>H</u>), 5.90 and 6.48 (each d and J=10 Hz, -COC<u>H</u>=C<u>H</u>-), 6.52 and 7.21 (each d and J=1.5 Hz, C_{11}-<u>H</u> and C_{13}-<u>H</u>). Subsequently, 12-methoxy-3-oxototara-1,8,11,13-tetraene (XXVIII)[2] was also converted to the corresponding phenol (IV); mp 201.5-202°C; IR: 3597, 3313, 1675 cm^{-1}; UV: λ_{max}^{EtOH} nm (ε): 223 (16,100), 285 (2,400); NMR ($CDCl_3$): 1.19 (s, C_4-(C<u>H</u>$_3$)$_2$), 1.17 and 1.23 (each d and J=6.5 Hz, -CH(C<u>H</u>$_3$)$_2$), 1.58 (s, C_{10}-C<u>H</u>$_3$), 5.95 and 6.53 (each d and J=10 Hz, -COC<u>H</u>=C<u>H</u>-), 6.72 and 7.21 (each d and J=3 Hz, C_{11}-<u>H</u> and C_{13}-<u>H</u>), 7.25 (s, -O<u>H</u>); via an epoxide (XXIX), an alcohol (XXX), and an α,β-unsaturated ketone (XXXI); IR: 1680 cm^{-1}; NMR: 5.75 and 6.35 (each d and J=10 Hz, -COC<u>H</u>=C<u>H</u>-). The synthetic III and IV were also shown to be not identical with natural shonanol by spectral comparisons.

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IR spectra were taken in chloroform and NMR spectra in carbon tetrachloride at 60 MHz unless otherwise specified. Their chemical shifts are presented in terms of δ values; s: singlet, bs: broad singlet, d: doublet, dd: double doublet, m: multiplet.

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2) T. Matsumoto, I. Tanaka, T. Ohno, and K. Fukui, This Letters, <u>1973</u>, 321.

3) Although the formula depicted represented only one enantiomer, they are taken to mean a racemate.

4) The β-configuration of hydroxyl group at the C-3 position was assigned by analogy with a similar reduction of 12-methoxy-3-oxopodocarpa-5,8,11,13-tetraene: M. Fetizon and G. Moreau, Bull. Soc. Chim. Fr., <u>1965</u>, 3479.

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