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SYNTHESIS OF (±)-12-HYDROXY-3-OXOTOTARA-1,8,11,13-TETRAENE
A PROPOSED STRUCTURE FOR SHONANOL

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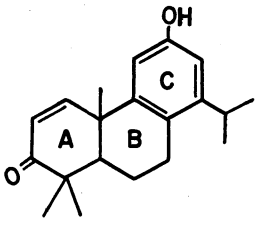
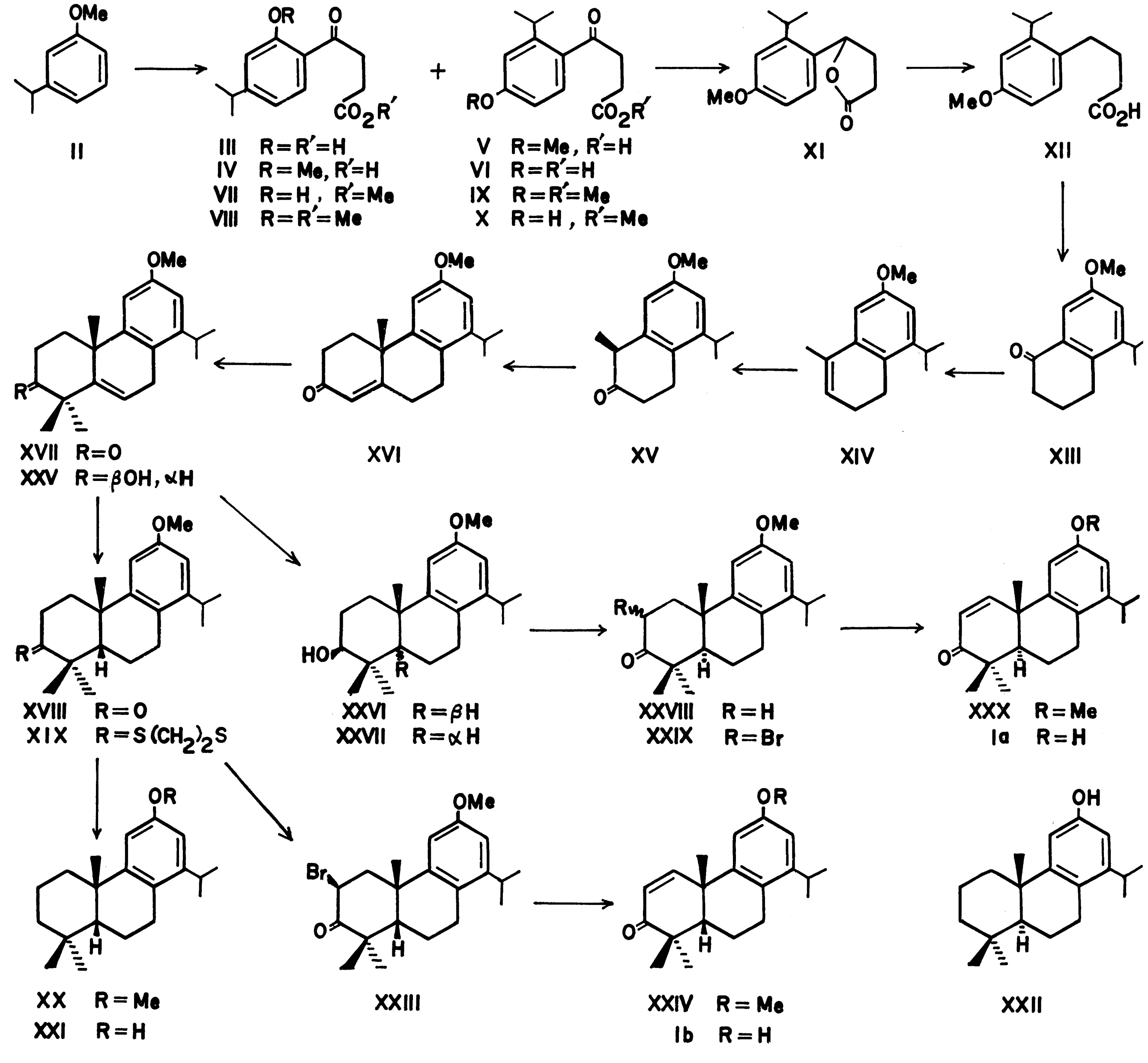
12-Hydroxy-3-oxototara-1,8,11,13-tetraene (Ia) and its cis-isomer (Ib) were synthesized from 3-isopropylanisole (II) via 5-isopropyl-7-methoxy-1-methyl-2-tetralone (XV) by the route of C→B→A ring construction. The spectral data of the synthetic Ia and Ib were different from those of natural shonanol.

Shonanol, a tricyclic diterpene phenol, was isolated from Libocedrus formosana by Lin and Liu.$^{1)}$ On the basis of spectral studies, the structure I was tentatively proposed for shonanol. Because I 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, we attempted a total synthesis of I in order to confirm the proposed structure. In this communication we wish to report the synthesis of 12-hydroxy-3-oxototara-1,8,11,13-tetraene (Ia) and its cis-isomer (Ib) by the route of C→B→A ring construction. The Friedel-Crafts reaction of 3-isopropylanisole (II) in methylene chloride or in nitrobenzene with succinic anhydride in the presence of anhydrous aluminium chloride gave a mixture of keto acids, which were separated into III (mp 172-174°C), IV (mp 117-118°C), V (mp 101-103.5°C), and VI (mp 199-200°C) by recrystallization, and then by column chromatography of their methyl esters (VII, VIII, IX, and X). Methylation of VII and X in acetone with methyl iodide and potassium carbonate gave VIII and IX, which were hydrolyzed with aqueous sodium hydroxide to give IV and V respectively. Similarly, VII and X were also converted to III and VI respectively. NMR in $CDCl_3$; IV: 1.27 (d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 2.71 and 3.30 (each t and J=6 Hz, $-(C\underline{H}_2)_2-$), 2.91 (m, J=7 Hz, $-C\underline{H}(CH_3)_2$), 3.90 (s, $-OC\underline{H}_3$), 6.78 (s), 6.83 (dd, J=8.5 and 1.5 Hz), and 7.73 (d, J=8.5 Hz) (aromatic protons), 10.57 (bs, $-CO_2\underline{H}$); V: 1.20 (d, J=6.5



I

Hz, -CH(CH_3)$_2$), 2.75 and 3.17 (each m, -(CH_2)$_2$-), 3.61 (m, J=6.5 Hz, -CH(CH_3)$_2$), 3.80 (s, -OCH_3), 6.69 (dd, J=9 and 2 Hz), 6.91 (d, J=2 Hz), and 7.62 (d, J=9 Hz)(aromatic protons), 10.0 (bs, -CO_2H). From the above spectral data, the structures of IV and V were identified as β-(4-isopropyl-2-methoxybenzoyl)- and β-(2-isopropyl-4-methoxybenzoyl)propionic acid respectively. Reduction of V with sodium borohydride, followed by treatment with dilute sulfuric acid gave a γ-lactone (XI, mp 60-60.5°C, IR: 1770 cm^{-1}). This was further converted to a butyric acid derivative (XII, mp 52°C) by hydrogenolysis using Pd-C (5%). Subsequently, treatment of XII in benzene with phosphorous pentachloride, followed by intramolecular cyclization with anhydrous stannic chloride, gave a 1-tetralone derivative (XIII, IR: 1670 cm^{-1}). The Grignard reaction of XIII with methylmagnesium iodide yielded the corresponding alcohol which by dehydration with dilute sulfuric acid gave a dihydronaphthalene derivative (XIV). This was then converted to 5-isopropyl-7-methoxy-1-methyl-2-tetralone (XV, IR: 1705 cm^{-1}) by oxidation with m-chloroperbenzoic acid and subsequent treatment with dilute sulfuric acid. Condensation of XV with methyl vinyl ketone in the presence of sodium amide gave a hexahydro-2-oxophenanthrene derivative (XVI, mp 135°C, IR: 1660 cm^{-1}) which was methylated with methyl iodide and potassium t-butoxide in t-butanol to give a 4,4-dimethyl derivative (XVII, IR: 1702 cm^{-1}). Catalytic hydrogenation of XVII over platinum oxide in acetic acid afforded a dihydro derivative (XVIII), IR: 1698 cm^{-1}; NMR: 0.77, 1.05, and 1.19 (each s, three methyls), 1.17 (d, J=6.5 Hz, -CH(CH_3)$_2$), 3.69 (s, -OCH_3), 6.51 and 6.58 (each d and J=2 Hz, aromatic protons), together with an alcohol which afforded XVIII by oxidation with Jones reagent.$^{2)}$ To know the stereochemistry of the A/B ring junction XVIII was converted to 12-hydroxy-5βH-totara-8,11,13-triene (XXI), NMR: 0.42, 0.91, and 1.09 (each s, three methyls), 1.08 and 1.14 (each d and J=6.5 Hz, -CH(CH_3)$_2$), 6.45 and 6.57 (each d and J=2.5 Hz, aromatic protons), by thioketalization with ethanedithiol in the presence of boron trifluoride, desulfurization with Raney Ni in boiling ethanol, and demethylation with sodium thioethoxide in dimethylformamide at 140°C, via XIX and XX, NMR: 0.40, 0.94, and 1.11 (each s, three methyls), 1.10 and 1.16 (each d and J=6.5 Hz, -CH(CH_3)$_2$), 3.69 (s, -OCH_3), 6.48 and 6.59 (each d and J=2 Hz, aromatic protons). In the NMR spectra the signals (0.40 and 0.42) due to methyl group at the C-4 position in XX and XXI suggested the presence of the cis A/B ring junction. Further, the IR spectrum of XXI was not identical with that of its trans-isomer (XXII).$^{3)}$ Therefore, the structure of XVIII was identified as 12-methoxy-5βH-3-oxototara-8,11,13-triene. Bromination of XVIII with pyridinium hydrobromide perbromide$^{4)}$ in chloroform-ethanol gave a bromo derivative (XXIII, IR: 1720 cm^{-1}; NMR: 4.83 (dd, J=14 and 4.5 Hz, -CHBr-)) which was then dehydrobrominated with lithium carbonate and lithium chloride in dimethylformamide to give an α,β-unsaturated keto derivative (XXIV), IR: 1665 cm^{-1}, NMR: 5.84 and 7.07 (each d and J=10.5 Hz, vinyl protons). Demethylation of XXIV with sodium thioethoxide gave 12-hydroxy-5βH-3-oxototara-1,8,11,13-tetraene (Ib), mp 170-172°C; IR: 3590, 3325, 1665, 1607, 1590 cm^{-1}; NMR in $CDCl_3$: 0.76, 1.20, and 1.41 (each s, three methyls), 1.08 and 1.19 (each d and J=4 Hz, $-CH(C\underline{H}_3)_2$), ca. 6.1 (bs, $-O\underline{H}$), 6.63 (s, aromatic protons), 5.90 and 7.12 (each d and J=10.5 Hz, vinyl protons). The IR and NMR spectra of Ib were different from those of natural shonanol.$^{1)}$ Subsequently, the preparation of trans-isomer (Ia) was carried out as follows. Reduction of XVII with lithium aluminium hydride gave an alcohol (XXV),$^{5)}$ which by catalytic hydrogenation over Pd-C (5%) in methanol at 60°C/50 atm. gave a mixture of dihydro derivatives (ca. 1:5 ratio). Since the NMR spectra of these minor (XXVI) and major alcohol (XXVII) showed signals at 0.41,



0.98, 1.18, and at 0.87, 1.04, 1.21, due to methyl groups at the C-4 and C-10 positions, the configurations of the A/B ring junction in XXVI and XXVII were assigned as cis and trans respectively. The latter was then oxidized with Jones reagent to give 12-methoxy-3-oxototara-8,11,13-triene (XXVIII), mp 123-125°C, IR: 1700 cm^{-1}; NMR: 1.18 (6H) and 1.35 (each s, three methyls), 1.20 and 1.24 (each d and J=7 Hz, $-\mathrm{CH(C\underline{H}_3)_2}$), 3.76 (s, $-\mathrm{OC\underline{H}_3}$), 6.68 (s, aromatic protons). This was further converted to the corresponding α,β-unsaturated ketone (XXX); IR: 1660 cm^{-1}; NMR: 5.89 and 7.48 (each d and J=10.5 Hz, vinyl protons), via a mixture of epimeric bromides (XXIX, IR: 1720 cm^{-1}). Finally, XXX was demethylated with boron tribromide to give Ia, mp 202.5-203°C, IR: 3593, 3325, 1660, 1612, 1593 cm^{-1}; UV: $\lambda_{\max}^{\mathrm{EtOH}}$ nm (ε); 225 (27400), 284 (3830), NMR in $\mathrm{CDCl_3}$: 1.18 and 1.22 (each d and J=7 Hz, $-\mathrm{CH(C\underline{H}_3)_2}$), 1.20, 1.24, and 1.43 (each s, three methyls), 5.99 and 7.54 (each d and J=10.5 Hz, vinyl protons), 6.66 and 6.79 (each d and J=3 Hz, aromatic protons). The spectral data of Ia were also different from those of natural shonanol.$^{1)}$ From the present study, we suggest that the proposed structure (I) of shonanol should be revised.

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REFERENCES

Although the formulas depicted represented only one enantiomer, they are taken to indicate a racemate. 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, t: triplet, m: multiplet.

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