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THE REACTION OF METHYL 7-OXODEHYDROABIETATE WITH PERBENZOIC ACID AND THE SYNTHESIS OF 11-METHOXYDEHYDROABIETANE

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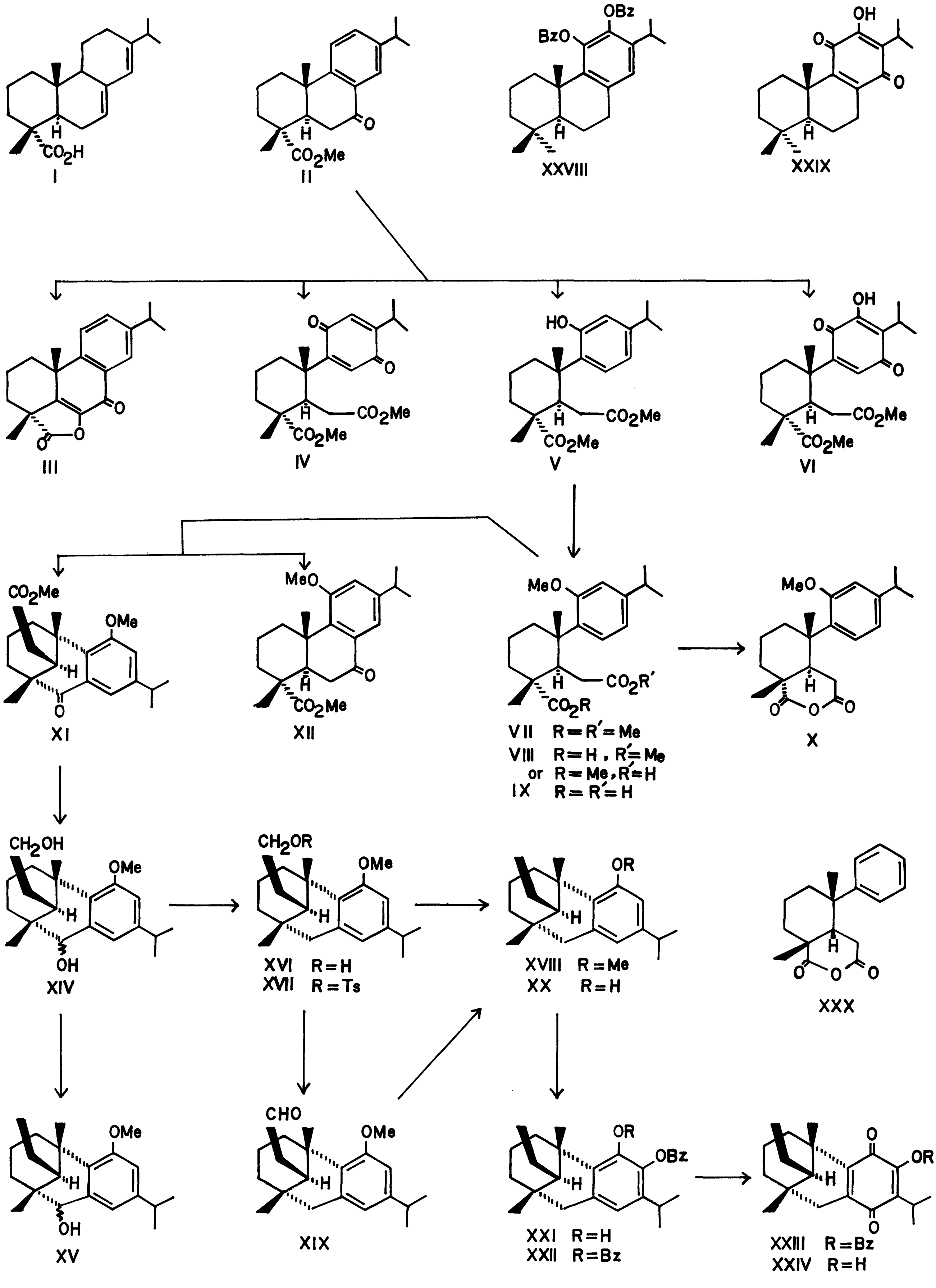
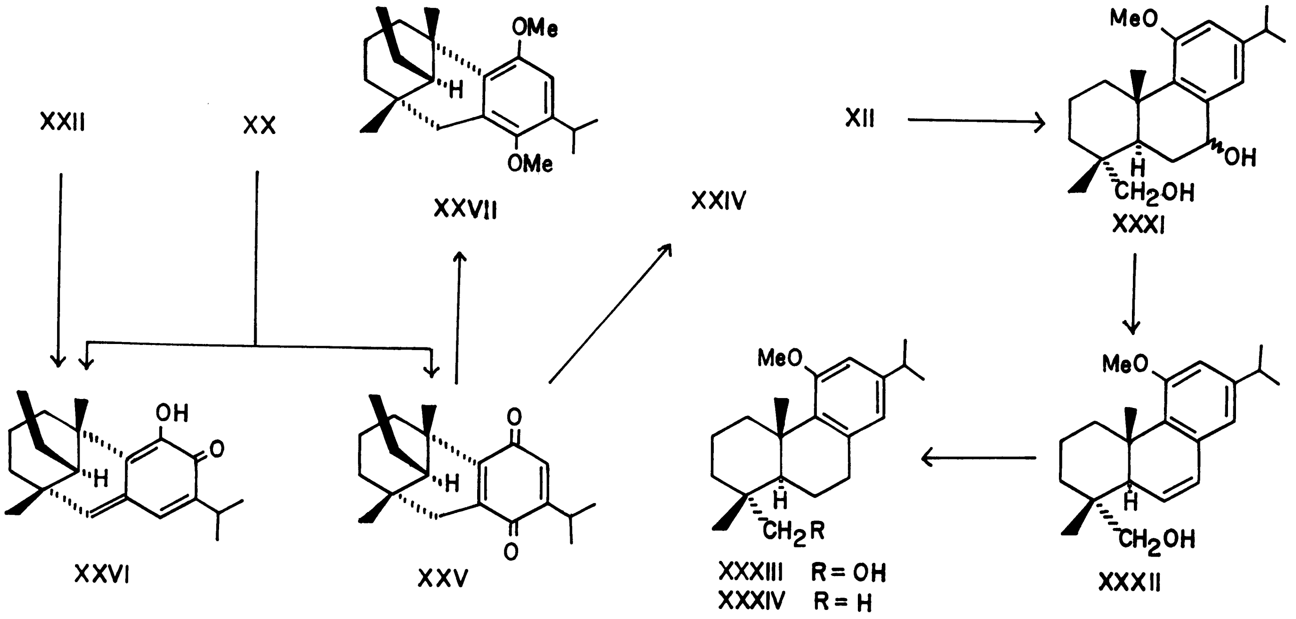
The oxidation of methyl 7-oxodehydroabietate with perbenzoic acid afforded a mixture of lactone (III), quinone (IV), hydroxyester (V), and hydroxyquinone (VI). The intramolecular cyclization of half acid (VIII) derived from V gave two ketoesters (XI and XII). The structures of XI and XII were assigned on the basis of their chemical and spectroscopic studies, and XII was converted into 11-methoxydehydroabietane (XXXIV).

During the course of synthetic work on natural diterpenes, the present authors attempted the conversion of abietic acid (I) into 11-hydroxydehydroabietic acid derivatives which seemed to be important intermediates for a new synthetic route of natural products possessing 11-hydroxyabietane skelton. In this communication$^{1)}$ we wish to report on the oxidation of methyl 7-oxodehydroabietate (II)$^{2)}$ derived from I, and on the synthesis of 11-methoxydehydroabietane (XXXIV). The oxidation of II with perbenzoic acid in chloroform was carried out at room temperature for 8.5 days. Subsequently, the crude product was refluxed for 2 hr with methanol containing concentrated hydrochloric acid to give four products, III (0.3 %), IV (5.0 %), V (46.6 %), and VI (1.3 %) along with the recovered II (22.6 %). The structures of these products were proved by their elemental analyses and the following spectral data. The enol lactone III$^{3,4)}$; mp 193-194°C; IR$^{5)}$: 1805, 1675, 1655 cm^{-1}; NMR$^{5)}$: 1.26 (d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.61 and 1.64 (each s, $2-\overset{|}{\underset{|}{C}}C\underline{H}_3$), 3.01 (m, J=7 Hz, $-C\underline{H}(CH_3)_2$), 7.49 (2H) and 8.15 (1H) (aromatic protons), The quinone IV; IR: 1720 1645 cm^{-1}; NMR: 1.11 (d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 1.17 and 1.24 (each s, $2-\overset{|}{\underset{|}{C}}C\underline{H}_3$), 2.27

(d, J=6 Hz, $\text{-}\mathrm{C\underline{H}_2CO_2}\text{-}$), 2.99 (m, J=7 Hz, $\text{-}\mathrm{C\underline{H}(CH_3)_2}$), 3.52 and 3.57 (each s, $2\text{-}\mathrm{CO_2C\underline{H}_3}$), 3.68 (t, J=6 Hz, $\text{-}\overset{|}{\mathrm{C}}\mathrm{\underline{H}CH_2CO_2}\text{-}$), 6.51 (s, $2\text{-}\overset{|}{\mathrm{C}}\mathrm{=C\underline{H}CO}\text{-}$). The hydroxyester V; mp 125-125.5°C; IR: 3450, 1720 cm^{-1}; NMR: 1.17 (d, J=7 Hz, $\text{-}\mathrm{CH(C\underline{H}_3)_2}$), 1.23 and 1.32 (each s, $2\text{-}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{C\underline{H}_3}$), 2.29 (d, J=6 Hz, $\text{-}\mathrm{C\underline{H}_2CO_2}\text{-}$), 2.78 (m, J=7 Hz, $\text{-}\mathrm{C\underline{H}(CH_3)_2}$), 3.33 and 3.46 (each s, $2\text{-}\mathrm{CO_2C\underline{H}_3}$), 3.97 (t, J=6 Hz, $\text{-}\overset{|}{\mathrm{C}}\mathrm{\underline{H}CH_2CO_2}\text{-}$), 6.31 (s, $\text{-}\mathrm{O\underline{H}}$), 6.67 (d, J=2 Hz), 6.71 (dd, J=2 and 8 Hz), and 7.15 (d, J=8 Hz) (aromatic protons). The hydroxyquinone VI; IR: 3370, 1720, 1660, 1630 cm^{-1}; NMR: 1.14 and 1.23 (each s, $2\text{-}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{C\underline{H}_3}$), 1.21 (d, J=7 Hz, $\text{-}\mathrm{CH(C\underline{H}_3)_2}$), 2.30 (d, J=6 Hz, $\text{-}\mathrm{C\underline{H}_2CO_2}\text{-}$), 3.20 (m, J=7 Hz, $\text{-}\mathrm{C\underline{H}(CH_3)_2}$), 3.52 and 3.60 (each s, $2\text{-}\mathrm{CO_2C\underline{H}_3}$), 3.68 (t, J=6 Hz, $\text{-}\overset{|}{\mathrm{C}}\mathrm{\underline{H}CH_2CO_2}\text{-}$), 6.39 (s, $\text{-}\overset{|}{\mathrm{C}}\mathrm{=C\underline{H}CO}\text{-}$), 7.43 (bs, $\text{-}\mathrm{O\underline{H}}$). The large pyridine-induced solvent shift ($\delta_{\mathrm{CDCl_3}} - \delta_{\mathrm{pyridine\text{-}d_5}} = -\ 0.77$ ppm) of the methine proton of isopropyl group in VI suggested the presence of a hydroxyl group at the position alpha to the isopropyl group, because the corresponding signal in IV showed no solvent-shift. The quinones, IV and VI, were also obtained by the similar oxidation of V with perbenzoic acid. The methylation of V with diazomethane gave the corresponding methyl ether (VII) which was then hydrolyzed with aqueous sodium hydroxide in ethanol to give a mixture of VIII, mp 137.5-138.5°C, and IX, mp 120-122°C. The diacid (IX) in refluxing acetic anhydride gave an anhydride (X), mp 167-168°C, IR: 1800, 1755 cm^{-1}. Subsequently, the treatment of half acid (VIII) in benzene with phosphorous pentachloride, followed by the intramolecular cyclization with anhydrous stannic chloride, gave two ketoesters, XI (66%, mp 80.5-81.5°C, IR: 1740, 1678 cm^{-1}) and XII (4 %, mp 114-115°C, IR: 1720, 1675 cm^{-1}), and a lactone XIII (11 %, mp 141-141.5°C, IR: 1750 cm^{-1}), which was recovered from an aqueous alkaline solution by acidification. The structural elucidation of XIII is in progress. The NMR spectra of these products showed the following signals; XI: 1.17 and 1.54 (each s, $2\text{-}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{C\underline{H}_3}$), 1.26 (d, J=7 Hz, $\text{-}\mathrm{CH(C\underline{H}_3)_2}$), 3.68 (s, $\text{-}\mathrm{CO_2C\underline{H}_3}$), 3.82 (s, $\text{-}\mathrm{OC\underline{H}_3}$), 6.93 and 7.63 (each d with J=2 Hz, aromatic protons), XII: 1.25 (d, J=7 Hz, $\text{-}\mathrm{CH(C\underline{H}_3)_2}$), 1.30 and 1.38 (each s, $2\text{-}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{C\underline{H}_3}$), 3.64 (s, $\text{-}\mathrm{CO_2C\underline{H}_3}$), 3.82 (s, $\text{-}\mathrm{OC\underline{H}_3}$), 6.92 and 7.59 (each d with J=2 Hz, aromatic protons), and XIII: 1.22 and 1.39 (each s, $2\text{-}\overset{|}{\underset{|}{\mathrm{C}}}\mathrm{C\underline{H}_3}$), 1.23 (d, J=7 Hz, $\text{-}\mathrm{CH(C\underline{H}_3)_2}$), 3.81 (s, $\text{-}\mathrm{OC\underline{H}_3}$), 6.79 (d, J=1.5 Hz), 6.82 (dd, J=1.5 and 8 Hz), and 7.12 (d, J=8 Hz) (aromatic protons). The structure of the major ketoester was assigned on the basis of the following evidence. The ketoester (XI) was reduced with $\mathrm{LiAlH_4}$ to afford the corresponding diol (XIV), the NMR spectrum of which showed signals at δ 3.59 ppm (2H, t, J=8 Hz) and at δ 4.40 ppm (1H, s) attributable to the protons attached to the carbons bearing the hydroxyl groups. Further,


I
II
XXVIII
XXIX
III
IV
V
VI
XI
XII
VII R = R′ = Me
VIII R = H, R′ = Me
or R = Me, R′ = H
IX R = R′ = H
X
XIV
XVI R = H
XVII R = Ts
XVIII R = Me
XX R = H
XXX
XV
XIX
XXI R = H
XXII R = Bz
XXIII R = Bz
XXIV R = H



the tosylation of XIV, followed by the reduction of the resulting tosylate with $LiAlH_4$ gave an alcohol (XV), mp 74.5-75.5°C. The NMR spectrum of XV showed a signal at δ 4.32 ppm (1H, s) due to the methine proton bearing the hydroxyl group and showed no signal at δ ca. 3.6 ppm. This means that the primary alcohol group in XIV was transformed into the methyl group in XV. Subsequently, the hydrogenolysis of XIV in acetic acid containing a small amount of concentrated sulfuric acid in the presence of Pd-C (30 %) was carried out at 50-60°C, and the resulting acetate was hydrolyzed with alcoholic sodium hydroxide to afford another alcohol (XVI). The NMR spectrum of XVI showed signals at δ 2.49 and 2.82 ppm (2H, AB q, J=17 Hz) due to the benzylic methylene protons and at δ 3.57 ppm (2H, t, J=8 Hz) due to the methylene protons carring the hydroxyl group, while no signal was observed at δ ca. 4.4 ppm. These spectral data strongly suggest that the ester and keto groups in XI are attached to the methylene group and to the carbons carring no hydrogen, respectively. Then, the hydroxymethylene group in XVI was converted into the methyl group in XVIII via the corresponding tosylate (XVII) by the method similar to that used for XV. Alternatively, the oxidation of XVI with chromic oxide-dipyridine complex, followed by the Huang-Minlon reduction of the resulting aldehyde (XIX, IR: 1718 cm^{-1}; NMR: 9.79 ppm) afforded XVIII along with its demethylated compound (XX). The demethylation of XVIII with sodium thioethoxide in dimethylformamide at 140-145°C afforded XX. To obtain further confirmation on the structure of XI and to know the reactivity of the benzene ring in XX, we attempted the conversion of XX into a dibenzoate (XXII) and into a hydroxyquinone (XXIV). The treatment[6] of XX with benzoyl peroxide in refluxing chloroform afforded a hydroxybenzoate (XXI), IR: 3570, 3380, 1735 cm^{-1}, which gave a dibenzoate (XXII), mp 163-164°C, IR: 1740, 1260 cm^{-1}. The physical and spectral properties of XXII were different from those of 11,12-dibenzoyloxydehydroabietane (XXVIII, mp 204-205°C, IR: 1750, 1250 cm^{-1}).[7] The hydroxybenzoate (XXI) in acetic acid containing a trace of concentrated sulfuric acid was oxidized with hydrogen peroxide (80 %) at room temperature to give a quinone (XXIII) as yellow crystals, mp 109.5-110.5°C, IR: 1742, 1660, 1650sh cm^{-1}. In the NMR spectra of XVIII-XXII the signals due to the benzylic methylene group appeared as the AB quartets centered at δ ca. 2.7 ppm, while the corresponding signal in XXIII appeared as a singlet at δ 2.32 ppm. The hydrolysis of XXIII with potassium hydroxide in methanol afforded a hydroxyquinone (XXIV); IR: 3360, 1673, 1636, 1610 cm^{-1}; UV: $\lambda_{max}^{CCl_4}$ 281 (ε 14500), 413 nm (ε 440); NMR: 1.01 and 1.42 (each s, $2\text{-}\overset{|}{\underset{|}{C}}C\underline{H}_3$), 1.24 (d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 2.38 (s, $-C\underline{H}_2\overset{|}{C}=$), 3.18 (m, J=7 Hz, $-C\underline{H}(CH_3)_2$), 7.18 (s, $-O\underline{H}$). The IR and NMR spectra of XXIV were also different from those of royleanone (XXIX).[8,9] Further, the oxidation of XX with Fremy's reagent[10] was carried out and the products were purified by means of column chromatography on silica gel to give a yellow quinone (XXV), IR: 1635 cm^{-1}; NMR: 0.99 and 1.33 (each s, $2\text{-}\overset{|}{\underset{|}{C}}C\underline{H}_3$), 1.10 (d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 2.32 (s, $-C\underline{H}_2\overset{|}{C}=$), 6.32 (d, J=1.5 Hz, $=C\underline{H}-$), and a hydroxyketone (XXVI), IR: 3350, 1640sh, 1620sh, 1610 cm^{-1}; NMR in CCl_4: 1.07 and 1.49 (each s, $2\text{-}\overset{|}{\underset{|}{C}}C\underline{H}_3$), 1.12 (d, J=7 Hz, $-CH(C\underline{H}_3)_2$), 6.31 and 6.71 (each s, $2{=}C\underline{H}-$), 7.45 (s, $-O\underline{H}$). The hydroxyketone (XXVI) was also obtained by the alkaline hydrolysis and subsequent air oxidation of XXII. The reductive methylation[8] of XXV gave a dimethyl ether (XXVII), NMR in CCl_4: 0.99 and 1.41 (each s, $2\text{-}\overset{|}{\underset{|}{C}}C\underline{H}_3$), 1.25 and 1.27 (each d with J=7 Hz, $-CH(C\underline{H}_3)_2$), 2.56 (s, $-C\underline{H}_2\overset{|}{C}=$), 3.21 (m, J=7 Hz, $-C\underline{H}(CH_3)_2$), 3.58 and 3.70 (each s, $2\text{-}OC\underline{H}_3$), 6.41 (s, aromatic proton). The quinone (XXV) was subjected to the Thiele-Winter reaction,[11] and the hydrolysis and subsequent oxidation of the product gave XXIV in a low yield. From the above experiments the structure of the major ketoester (XI) was fully confirmed. The similar result has also been reported by Ireland et al.[12] in the case of the intramolecular cyclization of an anhydride (XXX) in polyphosphoric acid.

Finally, in connection with XI the minor ketoester (XII) was also reduced with $LiAlH_4$ to the corresponding diol (XXXI) which was further dehydrated with p-toluenesulfonic acid in refluxing benzene to afford an alcohol (XXXII). The NMR spectrum of XXXII in CCl_4 showed signals at δ 5.80 and 6.34 ppm due to the two vinyl protons and at δ 3.02 and 3.30 ppm (AB q, J=11 Hz) due to the methylene protons carring the hydroxyl group. The catalytic reduction of XXXII in methanol in the presence of platinum oxide gave the corresponding dihydro derivative (XXXIII), NMR in CCl_4: 0.82 and 1.23 (each s, 2-$\overset{|}{\underset{|}{C}}C\underline{H}_3$), 1.16 (d, J=7 Hz, -$CH(C\underline{H}_3)_2$), 1.86 (s, -$O\underline{H}$), 3.02 and 3.33 (each d with J=11 Hz, -$C\underline{H}_2OH$), 3.72 (s, -$OC\underline{H}_3$), 6.35 (s, aromatic protons), which on the tosylation and subsequent reduction was transformed into 11-methoxydehydroabietane (XXXIV), NMR: 0.95 (6H) and 1.29 (3H) (each s, 3-$\overset{|}{\underset{|}{C}}C\underline{H}_3$), 1.23 (d, J=7 Hz, -$CH(C\underline{H}_3)_2$), 3.75 (s, -$OC\underline{H}_3$), 6.53 (s, aromatic protons).

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