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NOVEL SYNTHESIS AND ABSOLUTE CONFIGURATION OF SEMPERVIROL

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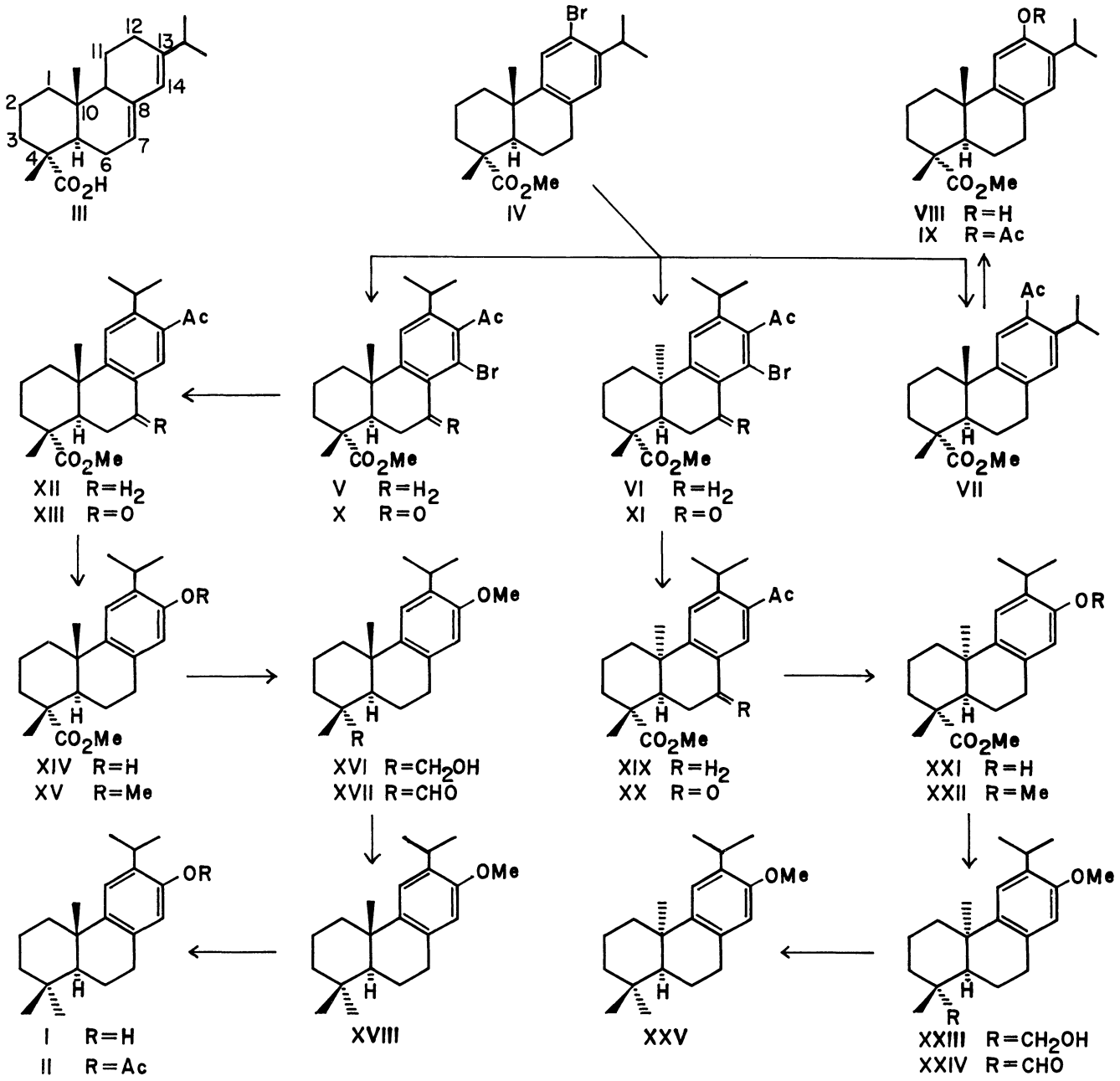
Friedel-Crafts reaction of methyl 12-bromodehydroabietate (IV) with acetyl chloride afforded methyl 13-acetyl-14-bromo-12-isopropyl-deisopropyldehydroabietate (V), its cis-isomer (VI), and methyl 12-acetyldehydroabietate (VII). Conversion of V to sempervirol (I) was successfully carried out. The absolute configuration of sempervirol has also been assigned.

Sempervirol (I), a novel diterpenoid phenol possessing an isopropyl group at the C-12 position, was isolated from Cupressus sempervirens by Mangoni and Caputo.[1] The structure of sempervirol has been confirmed by the total synthesis of racemic sempervirol (I) and its acetate (II).[2,3] In this communication we wish to report the novel synthesis and absolute configuration of the optically-active sempervirol (I). Friedel-Crafts acylation of methyl 12-bromodehydroabietate (IV)[4,5] derived from (-)-abietic acid (III), with acetyl chloride and aluminum chloride in methylene chloride was carried out. The crude product was purified by column chromatography and crystallization to give three acetyl derivatives; V (23%), mp 180-181°C, NMR:[6] 1.16 (d, J=6.5 Hz, $-CH(C\underline{H}_3)_2$), 1.20 (s, $C_4-C\underline{H}_3$ and $C_{10}-C\underline{H}_3$), 2.40 (s, $-COC\underline{H}_3$), 3.60 (s, $-CO_2C\underline{H}_3$), 7.10 (s, $C_{11}-\underline{H}$), VI (ca. 22%), NMR: 1.07 (s, $C_4-C\underline{H}_3$), 1.17 (s, $C_{10}-C\underline{H}_3$), 1.18 (d, J=6.5 Hz, $-CH(C\underline{H}_3)_2$), 2.40 (s, $-COC\underline{H}_3$), 3.56 (s, $-CO_2C\underline{H}_3$), 7.13 (s, $C_{11}-\underline{H}$), and VII (19%), mp 134-135°C, NMR in $CDCl_3$: 1.17 and 1.19 (each d and J=6.5 Hz, $-CH(C\underline{H}_3)_2$), 1.20 (s, $C_{10}-C\underline{H}_3$), 1.25 (s, $C_4-C\underline{H}_3$), 2.51 (s, $-COC\underline{H}_3$), 3.64 (s, $-CO_2C\underline{H}_3$), 7.04 (s, $C_{14}-\underline{H}$), 7.39 (s, $C_{11}-\underline{H}$). The acetyl derivative (VII) was converted[5] to the corresponding phenol (VIII), mp 157-159°C, and its acetate (IX). From the physical and spectral data of VII, VIII, and IX, the structure of VII was identified as methyl 12-acetyldehydroabietate.[5,7] Oxidation[8] of the bromoacetyl derivatives

(V and VI) with potassium permanganate and manganese sulfate in pyridine afforded the corresponding 7-oxo derivatives, X (mp 149.5-150.5°C) and XI respectively. The NMR spectra of X and XI showed signals due to the aromatic protons at δ 7.21 ppm and at δ 7.19 ppm respectively. These small paramagnetic shifts (V-X: 0.11 ppm and VI-XI: 0.06 ppm) suggested the absence of a proton at the C-14 position in V and VI. Debromination of V with hydrogen in methanolic potassium hydroxide in the presence of Pd-C (5%) or with n-butyl lithium in ether afforded an oil (XII), which was then oxidized with potassium permanganate to the 7-oxo derivative (XIII). In the NMR spectrum of XII signals due to the aromatic protons appeared at δ 7.11 and 7.19 ppm as singlets, indicating the absence of ortho- or meta-coupling between the aromatic protons. Further, the aromatic protons in XIII were also observed as singlets at δ 7.35 and 8.13 ppm. These spectral data suggested the presence of two aromatic protons at the C-11 and C-14 positions in XII. Baeyer-Villiger oxidation of XII with m-chloroperbenzoic acid and p-toluenesulfonic acid in 1,2-dichloroethane followed by alkaline hydrolysis of the resulting acetate gave a phenol (XIV), mp 136-137°C, NMR in $CDCl_3$: 1.16 (s, C_{10}-C$\underline{H}_3$), 1.20 (d, J=6.5 Hz, -CH(C$\underline{H}_3$)$_2$), 1.25 (s, C_4-C$\underline{H}_3$), 3.64 (s, -CO$_2$C$\underline{H}_3$), 4.85 (s, -O$\underline{H}$), 6.40 (s, C_{14}-$\underline{H}$), 7.03 (s, C_{11}-$\underline{H}$). Treatment of XIV with dimethyl sulfate and potassium carbonate in acetone afforded a methyl ether (XV), which on reduction with lithium aluminum hydride in ether gave an alcohol (XVI), mp. 94-95°C. Oxidation of XVI with chromic trioxide-pyridine complex afforded a formyl derivative (XVII), NMR: 9.13 (s, -C$\underline{H}$O), which was then subjected to Huang-Minlon reduction to give the corresponding 4,4-dimethyl derivative (XVIII), NMR: 0.93 (s, C_4=(C$\underline{H}_3$)$_2$), 1.13 (s, C_{10}-C$\underline{H}_3$), 1.14 (d, J=6.5 Hz, -CH(C$\underline{H}_3$)$_2$), 3.16 (m, J=6.5 Hz, -C$\underline{H}$(CH$_3$)$_2$), 3.70 (s, -OC$\underline{H}_3$), 6.30 (s, C_{14}-$\underline{H}$), 6.92 (s, C_{11}-$\underline{H}$). Demethylation of XVIII with sodium thioethoxide in refluxing dimethyl formamide afforded sempervirol (I), NMR: 0.93 (s, C_4=(C$\underline{H}_3$)$_2$), 1.14 (s, C_{10}-C$\underline{H}_3$), 1.20 (d, J=7 Hz, -CH(C$\underline{H}_3$)$_2$), 3.09 (m, J=7 Hz, -C$\underline{H}$(CH$_3$)$_2$), 4.29 (s, -O$\underline{H}$), 6.22 (s, C_{14}-$\underline{H}$), 6.93 (s, C_{11}-$\underline{H}$), which was characterized as its acetate (II), mp 91.5-92°C, $[\alpha]_D$+47° ($CHCl_3$) (lit.[1] mp 92-93°C, $[\alpha]_D$+51° ($CHCl_3$)). The IR spectrum of the synthetic acetate was identical in every respect with that published.[2] In the present study it seemed that no configurational change had occured at the C-4 position. Therefore, four types of stereoisomers (5αH-10βCH$_3$, 5βH-10αCH$_3$, 5αH-10αCH$_3$, and 5βH-10βCH$_3$) originated from the C-5 and C-10 positions were possible for V. By the comparison of the NMR spectra of V and its derivatives with those of the above four types of compounds reported[9,10] the configuration of V was assigned as the 5αH-10βCH$_3$. This

means that the absolute configurations of the C-5 and C-10 positions in sempervirol is identical with those in (-)-abietic acid, whose absolute configuration is known as III. Subsequently, the structural elucidation of VI was also carried out as follows. Debromination of VI with hydrogen afforded an ester (XIX), mp 100.5-101°C, which was then converted to the 7-oxo derivative (XX). The NMR spectrum of XIX showed two singlets due to the aromatic protons at δ 7.13 and 7.22 ppm, while that of XX showed the corresponding signals at δ 7.34 and 8.18 ppm. These data suggested that the aromatic protons in XIX were located at the C-11 and C-14 positions. Baeyer-



Villiger oxidation of XIX followed by alkaline hydrolysis gave a new phenol (XXI), mp 134.5-135°C, NMR in $CDCl_3$: 1.07 (s, C_4-C<u>H</u>$_3$), 1.17 (s, C_{10}-C<u>H</u>$_3$), 1.21 (d, J=7 Hz, -CH(C<u>H</u>$_3$)$_2$), 3.64 (s, -CO$_2$C<u>H</u>$_3$), 6.39 (s, C_{14}-<u>H</u>), 7.03 (s, C_{11}-<u>H</u>). Methylation of XXI afforded a methyl ether (XXII) which was further converted to a formyl derivative (XXIV), mp 150-152°C, NMR: 9.45 (s, -C<u>H</u>O), via the corresponding alcohol (XXIII). Huang-Minlon reduction of XXIV afforded the corresponding 4,4-dimethyl derivative (XXV), NMR: 0.36 (s, C_4-C<u>H</u>$_3$), 0.92 (s, C_4-C<u>H</u>$_3$), 1.12 (s, C_{10}-C<u>H</u>$_3$), 1.20 (d, J=6.5 Hz, -CH(C<u>H</u>$_3$)$_2$), 3.20 (m, J=6.5 Hz, -C<u>H</u>(CH$_3$)$_2$), 3.73 (s, -OC<u>H</u>$_3$), 6.35 (s, C_{14}-<u>H</u>), 6.97 (s, C_{11}-<u>H</u>). The chemical shifts of the aromatic protons in VI and its derivatives were in good accordance with those in the corresponding V and its derivatives, rather than those in VII and VIII (δ 6.60 and 6.79 ppm in $CDCl_3$). Further, in the NMR spectra of VI and its derivatives the chemical shifts (δ 1.07-0.31 ppm) of methyl protons at the C-4β position suggested the presence of the 5αH-10αCH$_3$ configuration.[9] From the above spectral data, VI was identified as methyl 13-acetyl-14-bromo-12-isopropyl-5αH-enantio-podocarpa-8,11,13-trien-19-oate.

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