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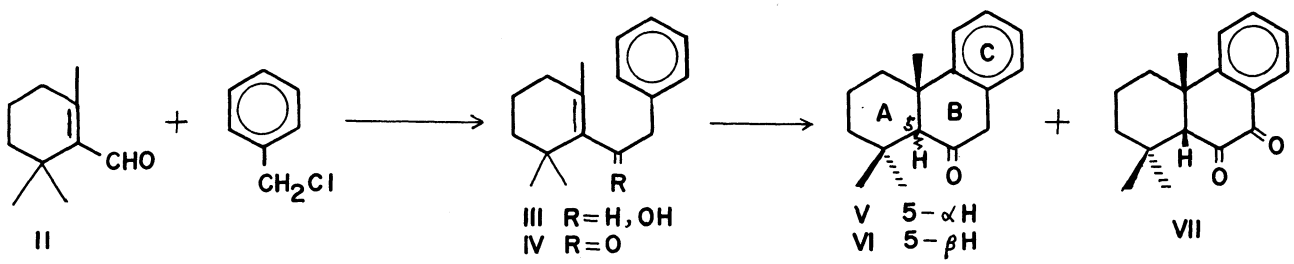
NEW SYNTHESIS OF (±)-SEMPERVIROL

Takashi MATSUMOTO, Shuji USUI, and Kenji FUKUI
Department of Chemistry, Faculty of Science, Hiroshima University
Higashisenda-machi, Hiroshima 730

The new synthesis of (±)-sempervirol (I) was described. Condensation of β-cyclocitral (II) with 4-isopropyl-3-methoxybenzyl chloride (XII) gave an alcohol (XIII), which by oxidation and subsequent intramolecular cyclization gave trans- and cis-fused 6-oxo compounds (XV and XVI). Both XV and XVI were respectively converted into (±)-I.

Sempervirol (I), a rare tricyclic diterpene phenol possessing an isopropyl group at the C-12 position, was isolated from Cupressus sempervirens by Mangoni and Caputo.[1] The total syntheses of the racemic sempervirol and its acetate have been achieved independently by Caputo and Mangoni[2] and Ghatak and Chatterjee.[3] Recently we also reported on a novel conversion of methyl 12-bromodehydroabietate to the optically-active sempervirol.[4] In the course of a continuing synthetic study on tricyclic diterpenes, we attempted the condensation of β-cyclocitral[5] (II: C_{10} unit as a moiety of ring A) and benzyl halide derivatives (C_{10} unit corresponding to ring C) followed by cyclization to the tricyclic ring-C aromatic diterpenes (C_{20} unit). This paper[6] will describe a convenient alternative synthesis of (±)-sempervirol.

As a model experiment the condensation of II with benzyl chloride in the presence of lithium$^+$ naphthalene$^-$ in tetrahydrofuran (under N_2 atmosphere, r.t., 3 hr) was carried out and the expected alcohol (III) was obtained in 79% yield. The alcohol (III) was then oxidized with chromic anhydride-pyridine complex (r.t., 5 hr) to the corresponding ketone (IV: 61%), IR:[7] 1690 cm^{-1}, NMR:[7] 1.04 (s, $-\dot{C}(CH_3)_2$), 1.54 (s, $-\dot{C}=\dot{C}CH_3$), 3.71 (s, $-COCH_2-$). Cyclization of IV with polyphosphoric acid (110°C, 1 hr) gave three ketones, V (7%), VI(73%), and VII(9%). The structures of these ketones were well supported by the following spectral data. V; IR: 1709 cm^{-1}, NMR: 1.08

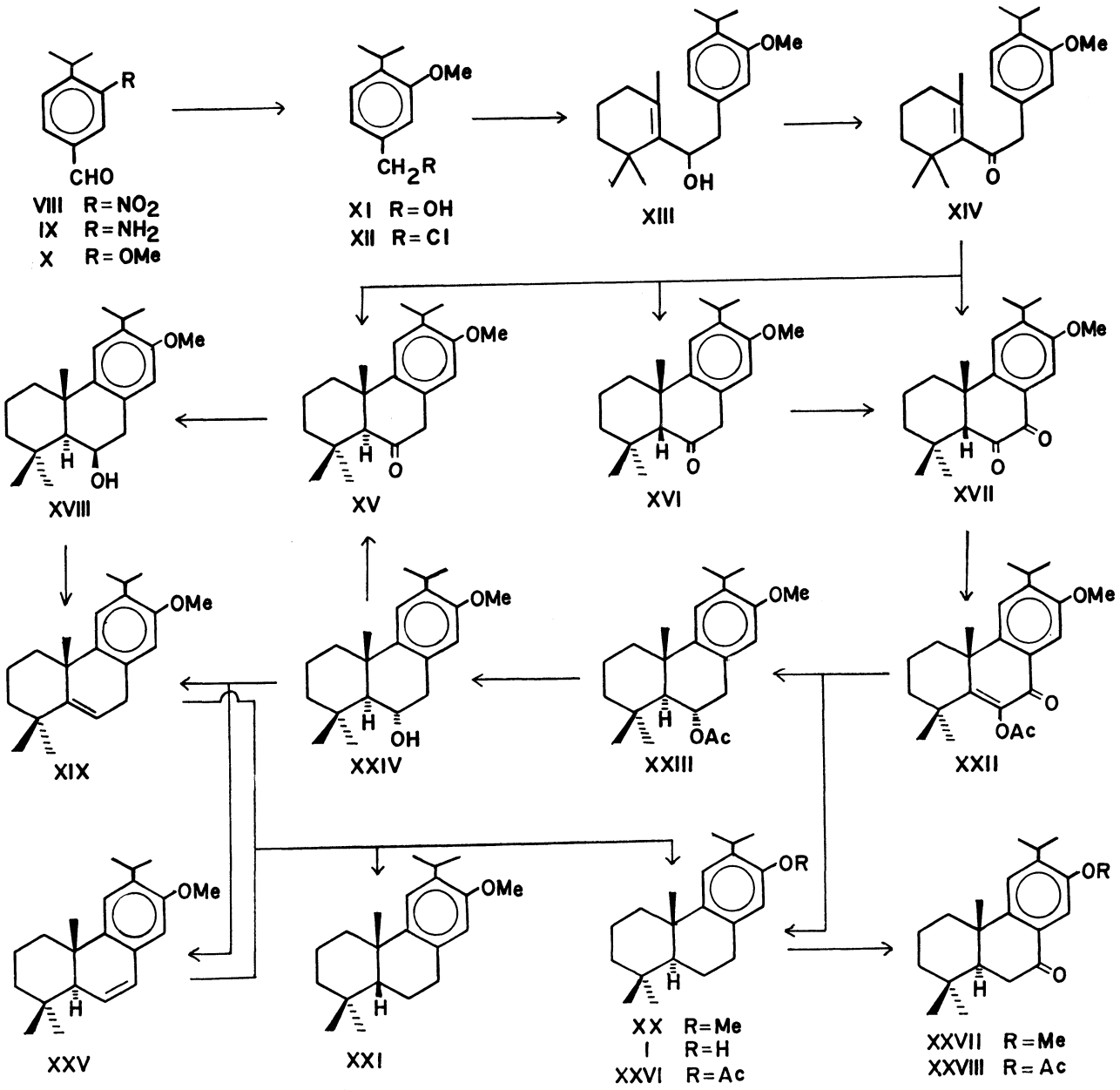


II

1.15, and 1.29 (each s, 3-$\overset{|}{C}CH_3$), 2.31 (s, C_5-H), 3.52 (s, -$COCH_2$-). VI; IR: 1692 cm^{-1}, NMR: 0.29 (s, $C_{4\alpha}$-CH_3), 0.91 and 1.08 (each s, $C_{4\beta}$-CH_3 and C_{10}-CH_3), 2.03 (s, C_5-H), 3.51 (bs, -$COCH_2$-). VII;[8,9] mp 124-127°C, IR: 1724, 1688 cm^{-1}, NMR: 0.38 (s, $C_{4\alpha}$-CH_3), 0.97 and 1.22 (each s, $C_{4\beta}$-CH_3 and C_{10}-CH_3), 2.59 (s, C_5-H). VII was also obtained by oxidation of VI with Jones reagent (r.t., 0.5 hr) in good yield (91%).

Subsequently, 4-isopropyl-3-methoxybenzyl chloride (XII), NMR: 1.19 (d, J=7 Hz, -CH($C\underline{H}_3$)$_2$), 3.84 (s, -OCH_3), 4.50 (s, -CH_2-), 6.76 (overlap), 6.80 (dd, J=2 and 8 Hz), and 7.09 (d, J=8 Hz) (aromatic protons), was prepared starting with 4-isopropyl-3-nitrobenzaldehyde (VIII)[10] via 3-amino-4-isopropylbenzaldehyde (IX), 4-isopropyl-3-methoxybenzaldehyde (X), and 4-isopropyl-3-methoxybenzyl alcohol (XI). Similar condensation of XII with II in the presence of $lithium^+$ $naphthalene^-$ gave an alcohol (XIII: 67%) which was further converted into the corresponding ketone (XIV: 49%), IR: 1690 cm^{-1}, NMR: 1.02 (s, -$\overset{|}{C}(CH_3)_2$), 1.18 (d, J=7 Hz, -CH($C\underline{H}_3$)$_2$), 1.53 (s, -$\overset{|}{C}$=$\overset{|}{C}CH_3$), 3.67 (s, -$COCH_2$-), 3.82 (s, -OCH_3), 6.60 (bd, J=8 Hz), 6.68 (bs, overlapped), and 7.00 (d, J=8 Hz) (aromatic protons). Treatment of XIV with polyphosphoric acid afforded two monoketones, XV (20%); IR: 1708 cm^{-1}, NMR: 1.07, 1.12, and 1.28 (each s, 3-$\overset{|}{C}CH_3$), 1.19 (d, J=7 Hz, -CH($C\underline{H}_3$)$_2$), 2.31 (s, C_5-H), 3.46 (s, -$COCH_2$-), 3.78 (s, -OCH_3), 6.39 and 7.03 (each s, aromatic protons), and XVI (46%), mp 98-99°C, IR: 1692 cm^{-1}, NMR: 0.30 (s, $C_{4\alpha}$-CH_3), 0.91 and 1.05 (each s, $C_{4\beta}$-CH_3 and C_{10}-CH_3), 1.20 and 1.23 (each d and J=7 Hz, -CH($C\underline{H}_3$)$_2$), 2.01 (s, C_5-H), 3.45 (s, -$COCH_2$-), 3.80 (s, -OCH_3), 6.43 and 7.04 (each s, aromatic protons), and a diketone (XVII: 5%), mp 119-121°C, IR: 1715, 1670 cm^{-1}, NMR: 0.40 (s, $C_{4\alpha}$-CH_3), 0.97 and 1.21 (each s, $C_{4\beta}$-CH_3 and C_{10}-CH_3), 1.25 and 1.28 (each d and J=7 Hz, -CH($C\underline{H}_3$)$_2$), 2.58 (s, C_5-H), 3.97 (s, -OCH_3), 7.22 and 7.47 (each s, aromatic protons), which was easily obtained by Jones oxidation (0°C, 0.5 hr) of XVI in 91% yield. Reduction of XV with lithium aluminum hydride in refluxing ether gave an alcohol (XVIII). The β-configuration of the hydroxyl group was supported by half-height width (8.5 Hz) of C_6-H signal at δ 4.58 ppm. XVIII was dehydrated with phosphorus oxychloride in pyridine (r.t., 14 hr) to give the 5-ene derivative (XIX: 71% from XV), NMR: 3.26 (d, J=4 Hz, -$\overset{|}{C}$=CH$\underline{CH}_2$-), 5.85 (t, J=4 Hz,

-C(=CHCH$_2$)-), which on catalytic hydrogenation with Pd-C in acetic acid gave (±)-sempervirol methyl ether (XX)[2], mp 57-57.5°C, and a small amount of the cis-isomer (XXI). Further, the cis-diketone (XVII) was also transformed into XX in the following manner. Treatment of XVII with sodium acetate in refluxing acetic anhydride (9 hr) gave an enol acetate (XXII: 70%), mp 119-120°C, IR: 1756, 1650 cm^{-1}. This was then submitted to catalytic hydrogenation using Pd-C in ethyl acetate in the presence of concentrated sulfuric acid to afford XX (18%) together with an acetate (XXIII: 77%), IR: 1723 cm^{-1}, NMR: 0.90, 1.08, and 1.18 (each s, 3-C(CH$_3$)), 1.18 (d, J=7 Hz, -CH(CH$_3$)$_2$), 1.95 (s, -OCOCH$_3$), 3.78 (s, -OCH$_3$), 5.40 (m, C$_6$-H), 6.41 and 6.91 (each s, aromatic protons). The α-configuration of the acetoxyl group was supported by the presence of one proton



multiplet (δ 5.40 ppm) with half-height width of 19 Hz in the NMR spectrum. Treatment of XXIII with lithium aluminum hydride in refluxing ether led to the corresponding alcohol (XXIV), from which XV was obtained by Jones oxidation. On the other hand, dehydration of XXIV with phosphorus oxychloride in pyridine gave a mixture of XIX and the 6-ene derivative (XXV) in an approximately 2:3 ratio (85% from XXIII). The mixture was then submitted to catalytic hydrogenation using Pd-C in acetic acid to give XX along with a very small amount of XXI. Finally, XX was demethylated with boron tribromide in methylene chloride (r.t., 2 hr) to give (±)-sempervirol (I: 91%) which was characterized as its acetate (XXVI). The IR and NMR spectra of the synthetic I and XXVI were respectively identical with those of the authentic samples.[4] Oxidation of XX and XXVI with chromic anhydride in acetic acid gave the corresponding 7-oxo derivatives; XXVII: mp 138.5-139°C, IR: 1665 cm^{-1}, and XXVIII, mp 134.5-135°C, IR: 1753, 1673 cm^{-1}.

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REFERENCES

1) L. Mangoni and R. Caputo, Tetrahedron Lett., 1967, 673; Gazz. Chim. Ital., 97, 908 (1967).

2) R. Caputo and L. Mangoni, Gazz. Chim. Ital., 97, 920 (1967); Chem. Abstr., 68, 13197y (1968).

3) U. R. Ghatak and N. R. Chatterjee, Tetrahedron Lett., 1967, 4783.

4) T. Matsumoto, S. Imai, T. Matsubayashi, F. Tsunenaga, and K. Fukui, Chem. Lett., 1972, 1159.

5) R. N. Gedye, P. C. Arora, and K. Deck, Can. J. Chem., 49, 1764 (1971). W. M. B. Könst, L. M. van der Linde, and H. Boelens, Tetrahedron Lett., 1974, 3175.

6) Although the formulas depicted represent only one enantiomers, they are taken to indicate racemates.

7) IR spectra were taken in $CHCl_3$ and NMR spectra in CCl_4 at 60 MHz, using tetramethylsilane as an internal standard. The chemical shifts are presented in terms of δ values.

8) J. Delobelle and M. Fetizon, Bull. Soc. Chim. Fr., 1961, 1632.

9) D. Nasipuri and M. Guha, J. Chem. Soc., 1962, 4248.

10) C. M. Atkinson and J. C. E. Simpson, J. Chem. Soc., 1942, 808.

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