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CHEMICAL TRANSFORMATION OF α-SANTONIN INTO SESQUITERPENE α-METHYLENE-γ-LACTONES, TUBERIFERINE AND ARTECALIN[1]

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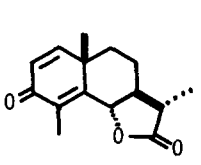
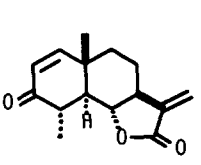
Some sesquiterpenes having α-methylene-γ-lactone moiety are worthy of attention to the cytotoxic and anti-tumor activities.[2] The transformation procedures of α-methyl-γ-lactones into α-methylene-γ-lactones have been reported by many workers.[3] Very recently, Grieco et al.[3] reported that α-methylene-γ-lactone compounds were prepared via phenylselenide derivatives in good yield under mild conditions. We applied the Grieco's method for the chemical transformation of α-santonin into some sesquiterpene α-methylene-γ-lactones.

In this paper, we wish to report the chemical transformation of (-)-α-santonin (I) into (+)-tuberiferine (II)[4] and (+)-artecalin (III).[5] α-Tetrahydrosantonin (IV), which was a reduction product of I, was chosen as a starting material because of the same absolute configuration at C 4,5,6,7 as tuberiferine and artecalin.



(I)



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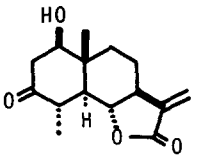

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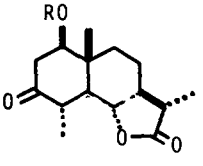

(IXa) R=H

(IXb) R=CH_3CO

Chemical Transformation of α-Santonin into Tuberiferine

Bromination-dehydrobromination of α-tetrahydrosantonin (IV) gave Δ^1-dihydro-

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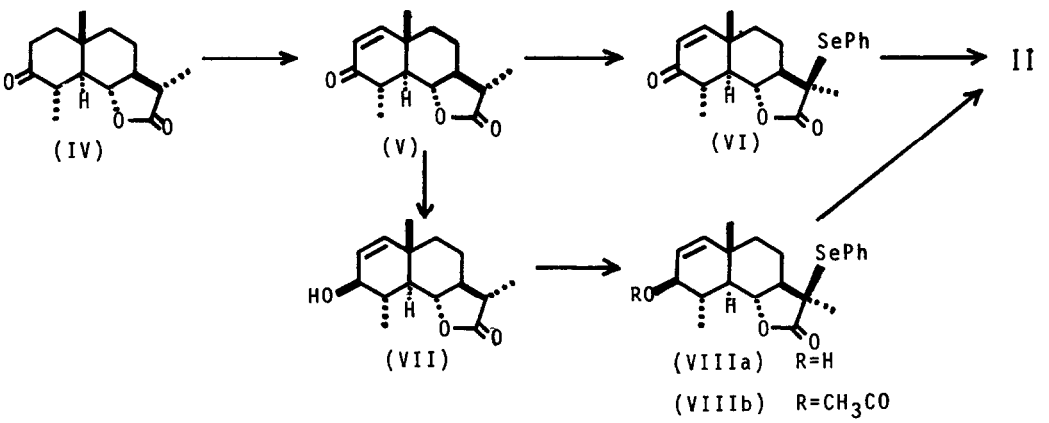
santonin (V).[6] According to the Grieco's method,[3] V was treated with two eq. molars of lithium diisopropylamide (LDA) and then an eq. molar of diphenyldiselenide to give a phenylselenide(VI), mp 158.5-161.5° in low yield (15% yield) [MS: m/e 404 $[M]^+$; NMR δ: 1.35 (3H, d, J=7 Hz; 4-CH_3), 1.51 (3H, s; 11-CH_3)]. Then, reduction of V with $LiAlH_4$ in THF at -10° gave stereoselectively a 3β-ol (VII), mp 181-183° [MS: m/e 250 $[M]^+$; NMR δ:3.78 (1H, d, J=9 Hz; 3-H), 5.50 (2H, s, 1,2-H)]. Phenylselenylation of VII gave a phenylselenide (VIIIa), oil [MS: m/e 406 $[M]^+$; NMR δ: 1.48 (3H, s, 11-CH_3), 7.22-7.68 (5H, m; Ph)] in 66.3% yield. VIIIa was converted to the acetate (VIIIb), mp 151.5-152.5°. Oxidation of VIIIa with activated MnO_2 afforded a ketonic compound(VI) in 87% yield, which was identical with VI. Treatment of VI with 30% hydrogen peroxide in THF containing a few drops of acetic acid at 0° furnished a α-methylene-γ-lactone com-



pound (II), mp 174-175°, quantitatively [MS: m/e 246 $[M]^+$; $[\alpha]_D^{25°}$ +3.7°; NMR δ: 1.17 (3H, s; 10-CH_3), 1.38 (3H, d, J=7 Hz; 4-CH_3), 3.97 (1H, t, J=10 Hz; 6-H), 5.45 and 6.11 (1H each, d, J=3 Hz; $\prec^{H}_{H}$), 5.91 and 6.73 (1H each, d, J=10 Hz; 1,2-H); IR cm^{-1}: ν_{CO} 1762 and 1663, $\nu_{C=C}$ 1625)]. The compound (II) was also prepared on the Jones oxidation of VIIIa in 56.4% yield.

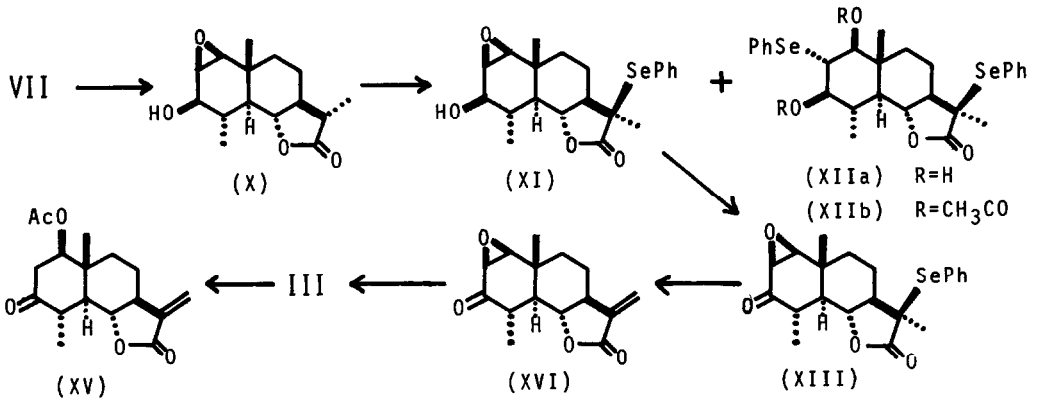
II was already presented as (+)-tuberiferine which was isolated from Sonchus Tuberifer Svent (compositae) by Barrera et al.[4] The IR, NMR and mp data of the compound (II) are not completly coincided with the data reported by Barrera et al. However, the IR and NMR spectrum of the natural (+)-tuberiferine were in good agreement with those of our compound (II).

Chemical Transformation of α-Santonin into Artecalin

The authors[7] have recently been succeeded the chemical transformation of (-)-α-santonin (I) into (+)-arsanin (IXa), 1β-hydroxy-α-tetrahydrosantonin, which was isolated from Artemisia santolina Schrenk by Sidyakin et al.[8] Geissman et al.[5] reported on the isolation of artecalin (III) from Artemisia californica Less. and the determination of its structure. Artecalin (dehydroarsanin) have a 11-exo-methylene-γ-lactone.

Stereoselective epoxidation of the 1-en-3β-ol (VII) with tert-butyl hydroperoxide in the presence of vanadyl acetyl acetonate gave a β-oxide (X), mp 206-209° (47% yield) together with the enone (V) (39% yield) [(X): MS: m/e 266 $[M]^+$; NMR δ: 3.03 (1H, d, J=3 Hz; 1-H), 3.33 (1H, dd, J=3, 2 Hz; 2-H), 3.44 (1H, dd, J= 10, 2 Hz; 3-H)]. X was treated with LDA and then diphenyldiselenide to give a phenylselenide (XI), mp 202-204° (81% yield) and together with a minor(2%yield) phenylselenohydrin (XIIa), oil [(XI): MS: m/e 422 $[M]^+$; NMR δ: 1.48 (3H, s, 11-CH_3), 7.25-7.70 (5H, m; Ph)]. XIIa was converted to the acetate (XIIb), mp 259-261° [MS: m/e 664 $[M]^+$; NMR δ: 1.48 (3H, s; 11-CH_3), 1.95 (6H, s; CH_3CO), 3.45 (1H, t, J=10 Hz; 2-H), 4.84 (1H, d, J=10 Hz; 1-H), 7.25-7.70 (10H, m; Ph)]. Oxidation of XI with activated MnO_2 gave a ketone (XIII), mp 191-192°, in 60% yield [MS: m/e 420 $[M]^+$; NMR δ: 1.48 (3H, s; 11-CH_3), 7.25-7.70 (5H, m; Ph); IR cm^{-1}: ν_{CO} 1768 and 1710]. XIII was treated with 30% hydrogen peroxide in THF containing a few drops of acetic acid to form (75% yield) a α-exomethylene-γ-lactone derivative (XIV) in the syn-elimination of selenoxide [(XIV), mp 152-154°; MS: m/e 262 $[M]^+$; NMR δ: 5.41 and 6.05 (1H each, d, J=3 Hz; $\measuredangle^{H}_{H}$); IR cm^{-1}: $\nu_{C=C}$ 1670]. Reductive cleavage of the β-epoxyketone (XIV) with zinc dust in benzene containing a few drops of acetic acid furnished 3-oxo-1β-hydroxy-5α-sant-11-en-6,12-olide (III)(95% yield), mp 210-212°(to a gel) [MS: m/e 264.1336 $[M]^+$ $C_{15}H_{20}O_4$ 264.1360, 246 $[M-H_2O]^+$; $[\alpha]_D^{22°}$ +40° ($CHCl_3$); NMR δ$(CD_3)_2CO$: 1.15 (3H, d, J=7 Hz; 4-CH_3), 1.15 (3H, s; 10-CH_3), 3.60 (1H, m, W=20 Hz; 1-H), 4.04 (1H, t, J=10 Hz; 6-H), 5.45 and 5.93 (1H each, d, J=3 Hz; $\measuredangle^{H}_{H}$); IR cm^{-1}: ν_{OH} 3490, ν_{CO} 1750 and 1695, $\nu_{C=C}$ 1673; UV λ_{max}^{EtOH} 207 nm (ε 9,520)]. The NMR spectral data of III was identical with that of natural (+)-artecalin which reported by Geissman et al.[5] III was converted to artecalin acetate (XV), mp 190-191° [MS: m/e 306 $[M]^+$; NMR δ: 1.16

(3H, s, 10-CH_3), 1.30 (3H, d, J=7 Hz; 4-CH_3), 2.04 (3H, s; CH_3CO), 2.43 (1H, AB-d, J=16 Hz; 2α-H), 2.85 (1H, AB-d, J=16 Hz; 2β-H), 3.90 (1H, t, J=10 Hz; 6-H), 4.92 (1H, dd, J=7, 12 Hz; 1-H)] with acetic anhydride and pyridine. These spectral data were also good coincided with those reported by Geissman et al.[5]



Catalytic reduction of XV with Pd-C catalyst gave IXb, mp 170-171°, which was identified by mixed mp and comparing its IR and NMR spectrum with that of arsanin acetate (IXb).[7]

Treatment of XV with sodium acetate in ethanol gave (+)-tuberiferine which was identical with the compound (II) as described above.

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