Application of Organoselenium Chemistry to the Total Synthesis of (±)-Tuberiferine

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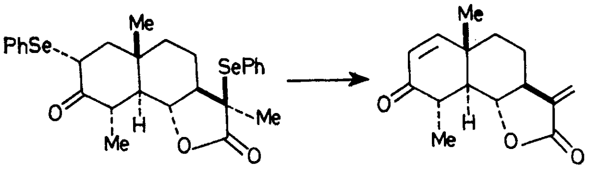
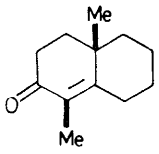
Summary The total synthesis of (±)-tuberiferine (**2**) is reported which employs the simultaneous introduction of the $\Delta^{1,2}$ double bond and the α-methylene unit *via* oxidation of the bis-selenide (**1**).

α-METHYLENE LACTONES can be prepared in high yield under mild conditions from appropriately substituted α-methyl-α-phenylseleno lactones.[1] The method is based on the well known fact that enolates react rapidly with phenylselenenyl chloride or diphenyl diselenide[2] and that alkyl phenyl selenoxides readily undergo *syn* elimination.[3] We report the application of organoselenium chemistry to the total synthesis of (±)-tuberiferine (**2**) *via* the key bis-selenenylated intermediate (**1**). In addition we demonstrate that α-methyl-α-phenylseleno lactones serve as protected α-methylene lactones which allow further chemical transformations within the same molecule. (+)-Tuberiferine, isolated from *Sonchus Tuberifer Svent* (compositae)[4] has recently been synthesized from (−)-α-santonin.[5]



(1) (2)

Acetalization of compound (**3**), obtained in 85% yield by the procedure of Heathcock and McMurry,[6] gave the olefin



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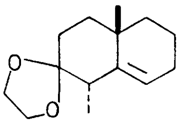
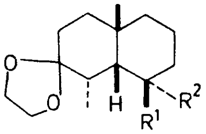
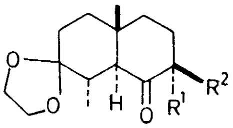


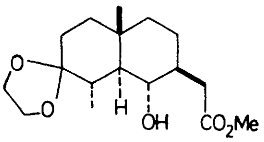
(4)



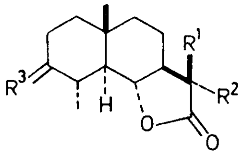
(5) $R^1 = OH, R^2 = H$
(6) $R^1R^2 = O$



(7) $R^1 = R^2 = H$
(8) $R^1 = CH_2CO_2Me; R^2 = H$
(9) $R^1 = H; R^2 = CH_2CO_2H$



(10)



(11) $R^1 = R^2 = H; R^3 = -O[CH_2]_2O-$
(12) $R^1 = Me; R^2 = H, R^3 = -O[CH_2]_2O-$
(13) $R^1 = PhSe; R^2 = Me; R^3 = O$

(**4**) in 56% isolated yield. Hydroboration of (**4**) provided in 90% yield the *cis*-decalol (**5**) which was oxidized with Collins reagent[7] to the *cis*-decalone (**6**). Epimerization (NaOMe–MeOH, reflux) of (**6**) afforded the pure *trans*-decalone (**7**) in 90% overall yield from (**5**). Kinetic enolate formation [lithium di-isopropylamide, tetrahydrofuran (THF), 0 °C] followed by the addition of a mixture of methyl bromoacetate and hexamethylphosphoric triamide (HMPA) (1 equiv.) gave the keto ester (**8**) (62%). Epimerization (NaOMe–MeOH) of (**8**) provided a new keto ester which was hydrolysed to the keto acid (**9**) (95%).

Stereoselective reduction of (**9**) [Li in liquid NH_3–THF (4 : 3)] followed by quenching with NH_4Cl, gave, after esterification, a 70% yield of the crystalline α-hydroxy ester (**10**), m.p. 114—115 °C. Treatment of (**10**) with toluene-*p*-sulphonic acid in refluxing benzene afforded the lactone (**11**) (89%), m.p. 186—187 °C [ν_{max} ($CHCl_3$) 1770 cm^{-1}]. Monomethylation[1] of (**11**) gave the lactone (**12**) (88%) [m.p. 198—199 °C; ν_{max} ($CHCl_3$) 1774 cm^{-1}; δ ($CDCl_3$) 0·94 (3H, s), 1·00 (3H, d), 1·14 (3H, d), and 4·00 (5H, m)].

Selenenylation [diphenyl diselenide–THF–HMPA (1 equiv.), −20 °C] of the lactone enolate derived from (**12**) followed by treatment with 3M hydrochloric acid gave stereospecifically the keto selenenylated lactone (**13**) [m.p. 146—147 °C; ν_{max} ($CHCl_3$) 1770 and 1705 cm^{-1}; δ ($CDCl_3$) 1·15 (3H, s), 1·20 (3H, d), 1·50 (3H, s), 4·33 (1H, t, *J* 10 Hz), and 7·2—7·8 (5H, m)] in 85% yield. The α-methyl-α-phenylseleno lactone (**13**) serves as a protected α-methylene lactone and permits further chemical transformations within the same molecule. This is not the case with the corresponding α-phenylselenomethyl lactone.[8] Introduction of the remaining α-phenylseleno group was accomplished at −78 °C by treatment of the preformed ketone enolate (lithium di-isopropylamide–THF, −78 °C) with phenylselenenyl chloride. A 76% yield of the bis-selenenylated compound (**1**) [ν_{max} ($CHCl_3$) 1775 and 1712 cm^{-1}; δ ($CDCl_3$)] 1·10 (3H, s), 1·31 (3H, d, *J* 7 Hz), 1·50 (3H, s), 4·15 (2H, m), and 7·2—7·8 (10H, m) was obtained. Oxidation of the bis-selenide (**1**) with ozone (2 equiv.) in CH_2Cl_2 at −78 °C followed by warming to room temperature over 1 h afforded (±)-tuberiferine (**2**) [m.p. 147—148 °C; ν_{max} ($CHCl_3$) 1763, 1665, and 1626 cm^{-1}; δ ($CDCl_3$) 1·18 (3H, s), 1·38 (3H, d, *J* 7 Hz), 3·98 (1H, t, *J* 10 Hz), 5·45 (1H, d, *J* 3 Hz), 5·90 (1H, d, *J* 10 Hz), 6·12 (1H, d, *J* 3 Hz), and 6·72 (1H, d, *J* 10 Hz)] in 60% yield whose n.m.r. and i.r. spectra were in accord with published data.[5]

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