Structure and Total Synthesis of Temisin

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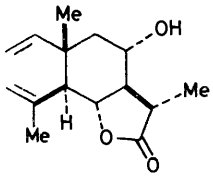
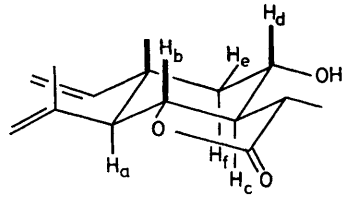
Summary The stereochemical features of the elemanolide sesquiterpene (+)-temisin (**1**) have been elucidated by n.m.r. analysis (250 MHz) and total synthesis.

DESPITE the fact that the sesquiterpene lactone temisin (**1**) was isolated in 1933[1] and that the gross structure was determined some eight years later,[2] no stereochemical information regarding the five chiral centres about the cyclohexane ring system and the chiral centre located on the γ-butyrolactone unit has been reported. We have now established, based on n.m.r. analysis of the natural material and total synthesis, that temisin possesses structure (**1**). Our interest in systems related to temisin stemmed from a programme in germacranolide total synthesis which required various *trans*-1,2-divinyl cyclohexane derivatives.[3]



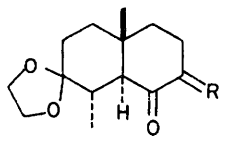
(1a)



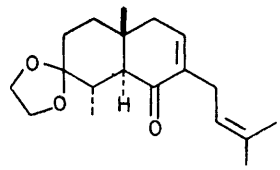
(1b)

Preliminary n.m.r. analysis at 250 MHz of natural temisin in $CDCl_3$ established the structural relationship of protons H_a—H_d. The n.m.r. spectrum revealed a one-proton doublet (J_{ab} 11 Hz) at δ 2·26 assigned to H_a, a one-proton triplet of doublets (J_{de} 4, $J_{cd} = J_{df}$ = 11 Hz) situated at δ 3·94 attributed to H_d, and a one-proton triplet ($J_{ab} = J_{bc}$ = 11 Hz) located at δ 4·12 which is assigned to H_b. These data are in complete agreement with the 'all-*trans*' diaxial arrangement of protons H_a—H_d shown in structure (**1b**).

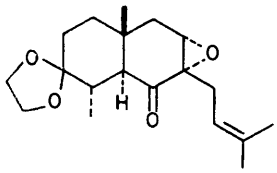
Having thus directly established four of the five chiral centres about the cyclohexane ring system, we proceeded to confirm the structure of natural temisin by direct comparison of its n.m.r. and i.r. spectra with those of a sample of racemic compound possessing the structure indicated by formula (**1**). We describe below the total synthesis of (±)-temisin which establishes the structure (**1**) for natural temisin.



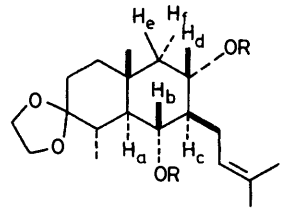
(2) R = H, H
(3) R = H, SePh
(4) R = β-SePh, α-$CH_2CH{=}CMe_2$



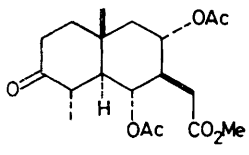
(5)



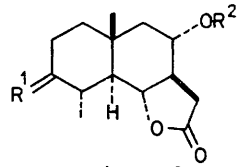
(6)



(7) R = H
(8) R = Ac



(9)

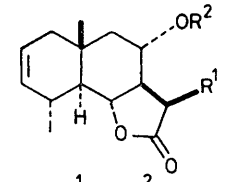


(10) R^1 = O, R^2 = H
(11) R^1 = O, R^2 = $SiMe_2Bu^t$

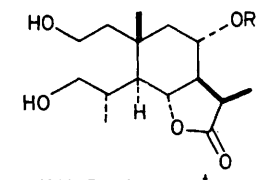
The previously described *trans*-fused ketone (**2**)[4] was subjected to kinetic enolate formation [lithium di-isopropylamide (LDA), tetrahydrofuran (THF), −78 °C]. Treatment of the resultant enolate with phenylselenenyl chloride gave, in 85% yield, the crystalline β-keto-selenide (**3**), m.p. 142—143 °C. Taking advantage of the enhanced acidity of the proton adjacent to both the carbonyl and phenylselenogroup, compound (**3**) was alkylated (LDA, hexamethyl phosphoric triamide, THF, −78 to 0 °C) with 1-bromo-3-methylbut-2-ene providing the ketone (**4**), m.p. 148—149 °C, 92% yield. The prenyl group serves as a latent two-carbon acetic acid residue which was required for elaboration of the *trans*-fused γ-lactone unit.

Oxidation of (**4**) (2·2 equiv. of 50% aq. H_2O_2, THF, 25 °C) was accompanied by elimination of benzeneselenenic acid and formation of the enone (**5**) (78%) [$\nu_{max}(CCl_4)$ 1687 cm^{-1}].[5] Epoxidation (Bu^tOOH, triton B)[6] of (**5**) in THF provided (91%) the α-epoxide (**6**) exclusively. Reduction[7] [excess of Li–NH_4Cl in liquid NH_3–THF (5 : 3)] of (**6**) resulted in a 50% yield of the diol (**7**) which, upon treatment with acetic anhydride in triethylamine containing 4-dimethylaminopyridine,[8] gave (95%) the diacetate (**8**), δ (CCl_4, 250 MHz) 4·94 (t, 1H, $J_{ab} = J_{bc}$ = 11 Hz), 4·70 (t of d, 1H, $J_{cd} = J_{df}$ = 11, J_{de} 4 Hz).

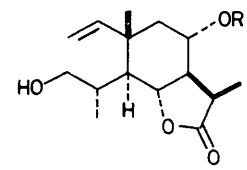
'Demasking' of the masked acetic acid residue was accomplished *via* ozonolysis (O_3, CH_2Cl_2, −78 °C, Me_2S), Jones oxidation, and esterification (CH_2N_2) to give the keto-ester (**9**), m.p. 116 °C in 94% overall yield. During the course of the oxidation the sensitive acetal was cleaved. Cleavage of the two acetate groups was carried out in scrupulously dried methanol using lithium methoxide. Upon subjecting the resultant diol to treatment with toluene-*p*-sulphonic acid in refluxing benzene, only one of the two possible lactones was produced: (**10**) (73%), m.p. 171—172 °C, $\nu_{max}(CHCl_3)$ 1782 and 1712 cm^{-1}. Protection of the remaining hydroxy group (Bu^tSiMe_2Cl, dimethylformamide, imidazole[9]) gave crystalline (**11**), m.p. 157—158 °C, in 78% yield.



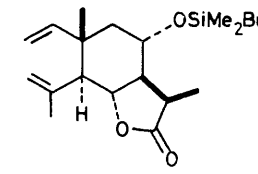
(12) R^1 = H, R^2 = $SiMe_2Bu^t$
(13) R^1 = Me, R^2 = $SiMe_2Bu^t$



(14) R = $SiMe_2Bu^t$



(15) R = $SiMe_2Bu^t$



(16)

With the major stereochemical and regiochemical problems resolved, we turned our attention to introduction of the *trans*-1,2-divinyl units. The tosyl hydrazone derived from the ketone (**11**) was subjected to a modification[3a] of the Shapiro olefin forming reaction [LDA, THF, −78 to 25 °C] to give the olefin (**12**) in 64% overall yield. Methylation[10] of the lactone enolate derived from (**12**) afforded in near quantitative yield crystalline (**13**), m.p. 94–95 °C. Ozonolysis of the $\Delta^{2,3}$ olefin [O_3, CH_2Cl_2–MeOH (1 : 1), −78 °C] followed by reduction (excess of $NaBH_4$, −78 to 0 °C) generated the diol (**14**) (91%). Treatment of (**14**) with *o*-nitrophenyl selenocyanate (4·0 equiv.) and tri-n-butylphosphine (4·0 equiv.) in THF (25 °C, 5 min) followed by

addition of 50% aqueous hydrogen peroxide (10 equiv.) gave, in 86% yield, the olefin (**15**).[11] Repetition of this one-step process provided the diene (**16**) (38%). Attempts to introduce both olefinic units simultaneously failed. Epimerization (LDA, THF, −78 °C; quench with NH_4Cl) at C-11 followed by cleavage of the silyl ether (Bu_4NF, THF)[9] gave (±)-temisin, m.p. 196—198 °C, in 70% overall yield from (**16**). The i.r. and n.m.r. (250 MHz) spectra of synthetic temisin were identical with those of (+)-temisin.

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