Total Synthesis of (±)-Diplodialide-A

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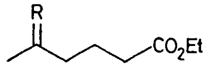
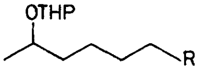
Summary The total synthesis of a ten-membered lactone, diplodialide-A, is described, involving the γ-selenenylation of the dianion of a β-ketolactone group followed by selenoxide elimination.

WE isolated a steroid hydroxylase inhibitor, diplodialide-A from the culture filtrate of *Diplodia pinea*.[1] The unique biological activity and structure have stimulated us to synthesize diplodialide-A and related compounds. We now report the total synthesis of (±)-diplodialide-A (**14**).

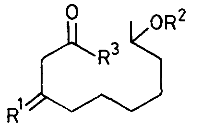
The key intermediate (**6**) was prepared by the reaction of the dianion[2] of ethyl acetoacetate with the tetrahydropyranyl ether of 1-bromohexan-5-ol (**5**). The bromide (**5**) was derived from ethyl 5-oxohexanoate (**1**) in 51% overall yield as follows: (i) $NaBH_4$ reduction of (**1**) in MeOH (−23 °C, 1 h), (ii) protection of the hydroxy group of (**2**) as its tetrahydropyranyl ether, (iii) $LiAlH_4$ reduction in ether [0 °C (10 min), then room temp. (50 min)], and (iv) bromination of the acid-sensitive alcohol (**4**) with CBr_4 and PPh_3 in pyridine–ether.[3] The protection of the keto group in (**6**) with ethanedithiol and $BF_3\cdot Et_2O$ in AcOH was accompanied by simultaneous removal of the tetrahydropyranyl group to afford the dithioacetal ester (**7**).



(1) R = O
(2) R = H, OH
(3) R = H, OTHP

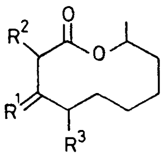


(4) R = OH
(5) R = Br

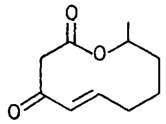


(6) R^1 = O, R^2=THP, R^3=OEt
(7) R^1 =-S[CH_2]$_2$S-, R^2=H, R^3=OEt
(8) R^1 =-S[CH_2]$_2$S-, R^2=H, R^3= OH
(9) R^1 =-S[CH_2]$_2$S-, R^2=H, R^3=2-pyridyl-S

THP = tetrahydropyran-2-yl



(10) R^1 =-S[CH_2]$_2$ S-, R^2= R^3= H
(11) R^1 = O, R^2=R^3=H
(12) R^1 = O, R^2= H, R^3= SePh
(13) R^1 = O, R^2= SePh, R^3=H



(14)

Saponification (1·3N KOH in 80% aq. MeOH) of the ester (**7**) gave the hydroxy acid (**8**), and this was converted into the corresponding thiol ester (**9**) {δ 3·22 (4H, s, -S[CH_2]$_2$-S-), 3·30 (2H, s, $-CH_2COS-$), 7·1 (1H, m), 7·5 (2H, m), and 8·4 (1H, m) (protons on α-substituted pyridine ring)} according to the method of Mukaiyama[4] in 66% overall yield from (**6**). A dilute xylene solution (5mM) of the thiol ester (**9**)[5] was refluxed for 25 h under argon to give the expected ten-membered lactone (**10**) (38% yield; M^+, *m/e* 260) and the dilactone (4·6% yield; M^+, *m/e* 520).† Removal of the dithioacetal group of the lactone (**10**) with *N*-bromosuccinimide in aqueous acetone[6] gave the β-ketolactone (**11**) in 82% yield. γ-Selenenylation of (**11**) was performed by generation of the dianion with lithium di-isopropylamide (2·6 equiv.) in n-hexane–tetrahydrofuran–hexamethylphosphoramide (*ca.* 7 : 4 : 1) followed by addition of benzeneselenenyl bromide (1·3 equiv.)[7] to give the γ-phenylselenolactone (**12**) in 38% yield. The n.m.r. spectrum of (**12**) confirmed the assigned structure: two doublets centred at 3·54 (2H, *J* 15 Hz; $-COCH_2CO-$) and a double doublet at 3·84 [1H, *J* 10 and 5 Hz; -COC*H*(SePh)-CH_2-]. It should be noted that the α-phenylseleno-derivative (**13**) (28%) was also produced.‡ Oxidation of selenoketone (**12**) with sodium metaperiodate afforded a product, in *ca.* 30% yield, identical in all aspects (n.m.r., i.r., u.v., and mass spectra, and t.l.c. and g.l.c. behaviour) with the naturally occurring (+)-diplodialide-A (**14**).[1]

Spectroscopic data for all compounds were in full accordance with the structure assigned.

We thank the Ministry of Education of Japan for a research grant.

(*Received*, *7th March* 1977; *Com.* 208.)

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† The lactonization of the hemithioacetal derivative of (**9**) under the same condition gave the corresponding lactone in very poor yield.

‡ The selenenylation of the dianion without hexamethylphosphoramide gave the α-phenylseleno-β-ketolactone (**13**) as the main product.

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