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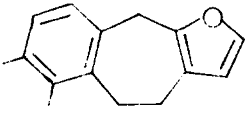
SYNTHESIS OF PALLESCENSIN-E : USE OF CROWN ETHER IN THE WADSWORTH PROCEDURE FOR OLEFIN FORMATION

By R. Baker and R.J. Sims

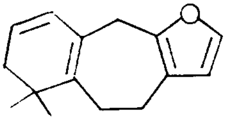
Department of Chemistry, The University, Southampton, SO9 5NH

Summary: The furanosesquiterpene, pallescensin-E has been prepared by a route involving reaction of a dimethyl 3-furylmethyl phosphonate anion with 2,3-dimethylbenzaldehyde in the presence of 15-crown-5; this reaction has been shown to have general applicability.

Pallescensin-E (1) a furanosesquiterpene containing the mono-cyclofarnesyl skeleton, has been isolated from the marine sponge, *Disidea pallescens*[1]. Its structure (1) was proposed by comparison with the co-occurring pallescensins-F (2) and -G (3) but has not been confirmed by synthesis. We have found that the addition of a catalytic quantity of a crown ether to the reaction of a phosphonate anion with a carbonyl compound greatly facilitates this reaction. We describe here a synthesis of pallescensin-E employing this reaction modification for the synthesis of stilbenes.



(1)



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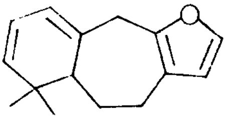
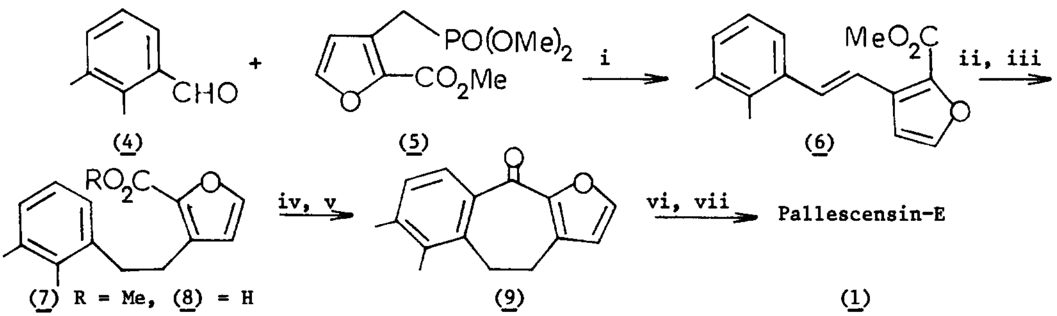


(3)

Hydrolysis of 2,3-dimethylbenzonitrile with 30% potassium hydroxide solution gave 2,3-dimethylbenzoic acid (m.p. 144-145.5°; 96%)[2] which was reduced with lithium aluminium hydride to give 2,3-dimethylbenzylalcohol (m.p. 63-6°; 62%). Oxidation of the alcohol with pyridinium chlorochromate gave 2,3-dimethylbenzaldehyde (4) (b.p. 90°/13 mm; 98%)[2].

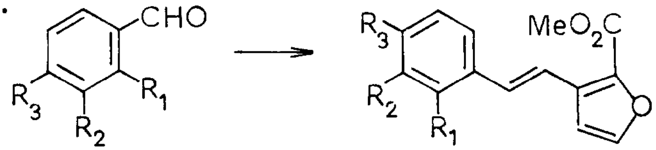
No reaction was obtained between the phosphonate (5) prepared by the method of Michael[3], and the aldehyde (4) following the manner of Seus and Wilson[4] and other literature conditions (e.g. NaOMe, 20-110°, DMF)[5]. The described *trans*-stilbene (6)* was obtained in moderate yield by the addition of 15-crown-5 (0.25 mol %) followed by heating at 80° for 1 h to give (6) (m.p. 64-5°; 45%) [$\delta(CCl_4)^{\dagger}$, 2.27(6H,s,2x$C\underline{H}_3$), 3.86(3H,s,$CO_2C\underline{H}_3$), 6.84(1H,d,J=2Hz, furan β-$\underline{H}$), 6.98-8.62(6H,m,furan α-$\underline{H}$, -$C\underline{H}$=$C\underline{H}$-,3x aromatic -$\underline{H}$]. Hydrogenation of the stilbene in the presence of $Rh(PPh_3)_3Cl$ gave the ethane (7) in 65% yield. Hydrolysis of the ester (7) with 10% sodium hydroxide solution gave the acid (8) (m.p. 174-6°; 69%). Reaction of this with thionyl chloride, followed by aluminium chloride in nitrobenzene gave the ketone (9) (m.p. 143-5°; 80°) [δ ($CDCl_3$) 2.33 and 2.36(6H,2xs,2x$C\underline{H}_3$), 2.70-2.96(2H,m,$C\underline{H}_2$), 3.04-3.26(2H,m,$C\underline{H}_2$), 6.46(1H,d,J=2Hz, furan β-$\underline{H}$), 7.08(1H,d,J=8Hz,C_8-$\underline{H}$), 7.50(1H,d,J=2Hz,furan α-H), 7.67(1H,d,J=8Hz,C_9-$\underline{H}$)]. Reduction of the ketone (9) was accomplished by reduction of the tosylhydrazone of (9) with



i) NaH, diglyme, 15-crown-5; ii) H_2, $Rh(Ph_3P)_3Cl$; iii) NaOH, H_2O; iv) $SOCl_2$, benzene; v) $AlCl_3$, $PhNO_2$; vi) $TsNHNH_2$, EtOH, TsOH; vi) $NaCNBH_3$, DMF.

sodium cyanoborohydride^6 to give pallescensin-E (1) (29%). Spectral data for the product are in complete agreement with the published data for pallescensin-E.

The formation of pallescensin-E by this route exemplifies the value of modification of the Wadsworth reaction conditions by the addition of crown ether. We have found this procedure to be of general applicability since phosphonate (5) has also been successfully reacted with a series of aldehydes. These reactions do not proceed, or yield at most a few percent of (14)-(17) without the addition of crown ether. We have found that consistently high yields are obtained from reactions of a number of aldehydes and ketones with phosphonates under these modified conditions^7.



	R_1	R_2	R_3		Yield
(10)	H	H	H	(14)	49%
(11)	H	H	Me	(15)	33%
(12)	Br	H	H	(16)	51%
(13)	H	OMe	OMe	(17)	54%

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REFERENCES AND NOTES

*No evidence for the formation of the *cis*-isomer was obtained (TLC, nmr)

†All spectroscopic and analytical data are in full agreement with the assigned structures

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