Cyclisation Reactions. Part 5.[1] Synthesis of Pallescensin A, a Furanoid Sesquiterpene by Cationic Cyclisation of an ω-Furyldiolefin and of the Corresponding Epoxy-olefin

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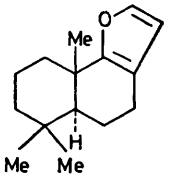
A biomimetic synthesis of pallescensin A (1), a furanoid sesquiterpene of natural origin is effected by concerted cyclisation of (6*E*)-9-(3-furyl)-2,6-dimethylnona-2,6-diene (2). The diene (2) has also been converted into a mono-epoxide (3) and the latter cyclised stereoselectively into 3-β-hydroxypallescensin A (4) which is subsequently deoxygenated to (±)-pallescensin A.

RECENTLY, Cimino *et al.*[2,3] have reported the isolation of a number of furanoid sesquiterpenes of unusual skeletons from the marine sponge, *Disidea pallescens*. Their structures have been established mainly from spectral evidence and mutual interconversions together with biogenetic considerations. Pallescensin A (1), a key member of this group may well originate from a concerted cyclisation of the acyclic precursor (2), a farnesane intermediate. For some time, we have been studying the biogenetic-type cyclisation of appropriate ω-aryldiolefins into naturally occurring tricyclic diterpenes[4-6] and pallescensin A appears to be an interesting substrate for such an investigation. We report here a stereoselective synthesis of this natural product from the diolefin (2), and also from the derived epoxy-olefin (3).



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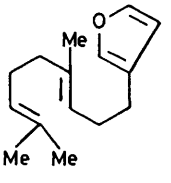

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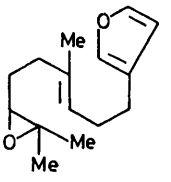

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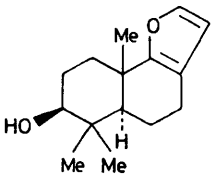
RESULTS AND DISCUSSION

(6*E*)-9-(3-Furyl)2,6-dimethylnona-2,6-diene (2) was prepared by coupling 3-furylmethylmagnesium chloride[7] with geranyl chloride in the presence of cuprous iodide.[8] The product proved to be almost exclusively the (6*E*)-isomer (>90%) by gas chromatography and had the expected n.m.r. spectrum. Cyclisation of the diene (2) with boron trifluoride etherate afforded an oil in good yield which consisted mainly of pallescensin A (1) (84%) and some olefinic impurity, which was easily separable by column chromatography over silver nitrate-impregnated silica gel. The identity with natural pallescensin A was established by comparison of i.r. and n.m.r. spectra (see below). The high stereoselectivity of the reaction is conceivably a result of a synchronous cyclisation and stands in contrast with our earlier observations[5] for the similar reaction of (6*E*)-9-phenyl-2,6-dimethylnona-2,6-diene, in which a considerable amount of *cis*-podocarpa-8,11-13-triene, along with other by-products, was formed through the intervention of a cyclic carbonium ion intermediate.[5]

An alternative and totally stereoselective synthesis of pallescensin A was also achieved from the epoxy-olefin (3) in a three-step procedure. The diolefin (2) was smoothly converted into the epoxy-olefin (3) by treatment with 1 mol of perbenzoic acid,[6] and (3) was cyclised with boron trifluoride etherate to give a crystalline alcohol (25%), which was identified as 3β-hydroxypallescensin A (4) on the evidence of its n.m.r. data (see Experimental section). The configurational assignment followed from the mode of concerted cyclisation.[6] The alcohol was oxidised by Jones reagent and the resultant ketone (5) converted into the tosylhydrazone. This was reduced with sodium borohydride[9] into a furanoid hydrocarbon, found to be identical with (±)-pallescensin A by comparison of i.r. and n.m.r. spectra; δ (CCl_4) 7.05 (1 H, d, *J* 2 Hz, 5′-H), 5.95 (1 H, d, *J* 2 Hz, 4′-H), 2.38 (2 H, t, 7-H_2), 2.12—1.40 (9 H, m, 4 × CH_2 + 5-H), 1.17 (3 H, s, 10-Me), and 0.93 and 0.91 (6 H, 2 × s, 4-Me_2), which agree with those reported for natural pallescensin A.[2]

While our work was in progress, Japanese workers reported[10] a synthesis of pallescensin A in its natural configuration by cyclisation of the cyclohexene derivative (6) which in turn was prepared from (*R*)-(−)-α-cyclocitral. The synthesis, however, is not stereoselective, the product being a mixture of *cis* and *trans* isomers in a 2 : 1 ratio.



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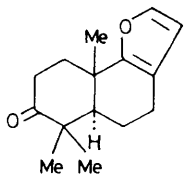

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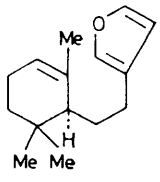

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EXPERIMENTAL

^{1}H N.m.r. spectra were taken with a Varian EM-390 90 MHz machine for solutions in [^{2}H]chloroform unless otherwise stated, with tetramethylsilane as internal standard. Petroleum refers to the fraction of b.p. 60—80 °C. Organic extracts were dried over sodium sulphate.

Geranyl Chloride.—Geranyl chloride was prepared from purified geraniol using triphenylphosphine and carbon tetrachloride in acetonitrile according to a known procedure.[6]

(6E)-9-(3-*Furyl*)-2,6-*dimethylnona*-2,6-*diene* (2).—To a solution of 3-furylmethylmagnesium chloride [from 3-furylmethyl chloride (7.5 g, 0.065 mol) and magnesium powder (7.8 g, 0.325 mol) in dry ether (130 ml)] at −10 °C was added cuprous iodide (1.0 g, 0.005 mol) in tetrahydrofuran (20 ml). Geranyl chloride (5.8 g, 0.034 mol) in tetrahydrofuran (30 ml) was next introduced dropwise into the dark solution. The mixture was left at room temperature for 12 h, decomposed with aqueous 20% ammonium chloride, and the ethereal layer separated. The aqueous layer was extracted with ether, the combined extracts dried and evaporated, and the residue distilled through a fractionating column to furnish the *diolefin* (2) as an oil, b.p. 95—100 °C at 0.05 mmHg (4.5 g, 32%) (Found: C, 82.7; H, 10.5. $C_{15}H_{22}O$ requires C, 82.6; H, 10.1%), δ 7.27 (1 H, d, *J* 2 Hz, 5′-H), 7.17 (1 H, s, 2′-H), 6.20 (1 H, d, *J* 2 Hz, 4′-H), 5.05 (2 H, m, 3-H + 7-H), 2.50—1.90 (8 H, m, 4 × CH_2), 1.70 (3 H, s, 6-Me), and 1.60 (6 H, s, 2 × Me).

Cyclisation of the Diolefin (2) : *Synthesis of Pallescensin A* (1).—Boron trifluoride–ether complex (10 mg) in dry methylene chloride (2 ml) was added to a solution of the foregoing diolefin (57 mg) in methylene chloride (8 ml) with stirring at room temperature. After 15 min, the dark red solution was decomposed with cold water, the methylene chloride layer separated, washed with water and aqueous sodium bicarbonate solution, dried, and the solvent evaporated. The residual red oil (55 mg) was absorbed on a column of alumina (5.0 g) and eluted with petroleum to furnish a colourless oil (38 mg) which consisted of two components in an 84 : 16 ratio as determined by gas chromatography (on a Carbowax 20 M column). The mixture was rechromatographed over 10% silver nitrate-impregnated silica gel (2.0 g). Elution with benzene–petroleum (15 : 85) afforded (±)-*pallescensin A* (1) (30 mg, 52%) as a colourless oil, b.p. 90 °C at 0.05 mmHg (Found: C, 82.3; H, 10.1. Calc. for $C_{15}H_{22}O$: C, 82.6; H, 10.1%). For the n.m.r. spectrum, see above.

(6E)-2,3-*Epoxy*-9-(3-*furyl*)-2,6-*dimethylnon*-6-*ene* (3).—A solution of perbenzoic acid (1.38 g, 0.01 mol) in chloroform (40 ml) was added to the diolefin (2) (2.18 g, 0.01 mol) in chloroform (5 ml) at 0—5 °C. The mixture was left in the refrigerator for 8 h and then worked up in the usual way.[6] The product showed two main spots on t.l.c., the upper one corresponding to the unreacted diolefin and the lower to the epoxy-olefin. It was absorbed on activated alumina and eluted with petroleum. After an initial fraction of the diolefin, the *epoxy-olefin* (3) (1.75 g, 75%), homogeneous on t.l.c., was eluted (Found: C, 76.5; H, 9.7. $C_{15}H_{22}O_2$ requires C, 76.9; H, 9.4%); δ (CCl_4) 7.20 (1 H, d, *J* 2 Hz, 5′-H), 710 (1 H, s, 2′-H), 6.17 (1 H, d, *J* 2 Hz, 4′-H), 5.00 (1 H, t, 7-H), 2.75—1.85 (9 H, m, 4 × CH_2 + 3-H), 1.70 (3 H, s, 6-Me), and 1.24 and 1.21 (6 H, d, 2 × Me).

3β-*Hydroxypallescensin A* (4).—To an ice-cooled solution of the preceding epoxide (1.5 g, 6.4 mmol) in dry methylene chloride (90 ml) was added boron trifluoride–ether complex (0.20 mg) under nitrogen. The mixture was stirred for 20 min at 0 °C and then diluted with water. The methylene chloride extract was washed with water and aqueous sodium bicarbonate, dried, and evaporated to yield a red gum (1.3 g) showing several spots on t.l.c. It was chromatographed on silica gel (50 g) using benzene–petroleum as eluant. After an initial fraction of oily material, a crystalline solid (0.35 g) was eluted with benzene–petroleum (25 : 75) and recrystallised from ether–petroleum to afford the *alcohol* (4) as colourless plates, m.p. 125—126 °C (Found: C, 76.7; H, 9.7. $C_{15}H_{22}O_2$ requires C, 76.9; H, 9.4%); δ 7.18 (1 H, d, *J* 2 Hz, 5′-H), 6.12 (1 H, d, *J* 2 Hz, 4′-H), 3.33 (1 H, t, *J* 8 Hz, 3-H), 2.48 (2 H, t, *J* 7 Hz, 7-H_2), 2.20 (1 H, m, 5-H), 1.79—1.38 (6 H, m, 3 × CH_2), 1.56 (1 H, s, OH, exchangeable with D_2O), and 1.19, 1.07, and 0.89 (9 H, 3 × s, 3 × Me); *m/e* 234 (M^+, 42%), 219 (100), 201 (83), 175 (10), 159 (10), 147 (28), 133 (18), 119 (13), 105 (12), 91 (18), and 77 (15); $\nu_{max.}$ 3 620 cm^{-1}.

3-*Oxopallescensin A* (5).—To a solution of the preceding alcohol (0.177 g) in acetone (7 ml) was added chromic acid in aqueous sulphuric acid dropwise until the green colour was replaced by red. The mixture was diluted with water and the organic matter was taken up in ether. After the usual work-up, a yellow gum (157 mg) was obtained which was absorbed on a column of activated alumina (6.0 g) and elution with benzene–petroleum (15 : 85) afforded 3-*oxopallescensin A* (5) (86 mg), m.p. 102 °C (from petroleum) (Found: C, 77.6; H, 8.9. $C_{15}H_{20}O_2$ requires C, 77.6; H, 8.6%); $\nu_{max.}$ ($CHCl_3$) 1 700 cm^{-1}; δ 7.23 (1 H, d, *J* 2 Hz, 5′-H), 6.15 (1 H, d, *J* 2 Hz, 4′-H), 2.70—2.35 (4 H, m, 2-H_2 + 7-H_2), 2.25 (1 H, t, *J* 7 Hz, 5-H), 2.00—1.50 (4 H, m, 2 × CH_2), and 1.24, 1.16, and 1.12 (9 H, 3 × s, 3 × Me). Further elution of the column with benzene–petroleum (25 : 75) afforded the starting alcohol (60 mg).

Pallescensin A.—The foregoing ketone (45 mg) was converted into the tosylhydrazone (60 mg), m.p. 170 °C (from methanol) (Found: C, 65.7; H, 7.1; N, 6.8. $C_{22}H_{28}N_2O_3S$ requires C, 66.0; H, 7.0; N, 7.0%). A solution of the tosylhydrazone (58 mg) and sodium borohydride (200 mg) in methanol (5 ml) was refluxed for 8 h. After removal of methanol, the residue was diluted with water and the organic matter extracted with petroleum (b.p. 40—60 °C). The petroleum extract was passed through a column of activated alumina (2.5 g) and the eluant on evaporation furnished a colourless oil (18 mg, 54%), identified as pallescensin A (Found: C, 82.4; H, 10.4. Calc. for $C_{15}H_{22}O$: C, 82.6; H, 10.1%); $\nu_{max.}$ (neat) 2 932, 2 920, 2 850, 1 495, 1 445, 1 380, 1 365, 1 355, 1 180, 1 145, 1 055, 875, 830, 815, 760, 715, 690, and 680 cm^{-1}. The n.m.r. spectrum was identical with that of natural pallescensin A (see above).

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