The Chemistry of Fungi. Part 75.[1] A Partial Elaboration of the Rosane System from Podocarpic Acid

By **C. George De Grazia** and **W. Basil Whalley,*** The School of Pharmacy, The University, London WC1N 1AX

In an approach to the synthesis of the rosane system [type (1)], 7-ethyl-*O*-methylpodocarpic acid (2; R^1 = Et, R^2 = CO_2H) was converted by a Birch reduction into 7-ethyl-6-methoxy-1α,4aβ-dimethyl-1,2,3,4,4a,5,8,9,10,10aα-decahydrophenanthrene-1β-carboxylic acid (3; R = H). After esterification, the enolic methoxy-group was removed to yield the αβ-unsaturated 6-ketone (4), which was hydrogenated to the ketone (5; R = CO_2Me). Reduction of the derived ethylene acetal (7; R = CO_2Me) gave (7; R = CH_2OH), which was deacetalised and acetylated to yield the acetate (6; R = CH_2OAc). Alkylation of (6; R = CH_2OAc) with methyl-lithium–methyl iodide gave the ketone (8) which probably has the requisite C-13 (terpene numbering) stereochemistry of the rosane system.

Deoxypodocarpic acid (9) was reduced to the dihydrobenzenoid system (10), which was hydrogenated to the 8,9-olefin (11). A solution of (11) in sulphuric acid gave 1α,4bβ-dimethylperhydro(10aα*H*)phenanthrene-1β,4aβ-carbolactone (12) (*cf.* rosenonolactone).[2]

THE fungal metabolites of the rosenonolactone group[2] offer an interesting synthetic challenge. The work described in this paper was initiated with the object of deriving the rosane nucleus [type (1)]. As will be apparent, the project was abandoned, but a selection of our results seems worthy of record.

[1] Part 74, S. M. Afzal, R. Pike, N. H. Rama, I. R. Smith, E. S. Turner, and W. B. Whalley, preceding paper.

[2] See *e.g.* W. B. Whalley, B. Green, D. Arigoni, J. J. Britt, and C. Djerassi, *J. Amer. Chem. Soc.*, 1959, **81**, 5520.

The starting material was the readily available podocarpic acid. Methyl 7-acetyl-*O*-methylpodocarpate [3] (2; $R^1 = COCH_3$, $R^2 = CO_2Me$) was reduced directly by the Wolff–Kishner process to the 7-ethyl derivative (2; $R^1 = Et$, $R^2 = CO_2Me$) or indirectly by sodium borohydride to methyl *O*-methyl-7-(1-hydroxyethyl)podocarpate [2; $R^1 = CH(OH)CH_3$, $R^2 = CO_2Me$], and thence by lithium–liquid ammonia to (2; $R^1 = Et$, $R^2 = CO_2Me$). The ether (2; $R^1 = Et$, $R^2 = CO_2Me$) could not be reduced under the usual Birch conditions, nor by sodium or lithium and t-butyl alcohol in tetrahydrofuran and liquid ammonia.[4] However, after numerous trials, reduction [5] using lithium–t-pentyl alcohol–*O*-methylpodocarpic acid in the ratios 40 : 40 : 1 in triethylamine gave moderate yields and satisfactory reproducibility provided that the scale of reduction was restricted to 1 g quantities of acid. The structure (3; R = H) was in accord with the n.m.r. spectrum (see Experimental section) (absence of vinylic protons) and the u.v. spectrum (non-conjugated diene). Esterification of (3; R = H) gave the ester (3; R = Me).

Hydrolysis of the enolic ether grouping in (3; R = Me) gave a product which was formulated as the αβ-unsaturated ketone (4) on the basis of spectral evidence (see Experimental section), with the probable 8β-configuration. The ethyl residue was assigned the equatorial (α-) configuration on the assumption that the thermodynamically more stable orientation would result from hydrolysis of the enol. Even under optimum conditions a major by-product in this reduction was methyl 7-ethylpodocarpate, arising from the cleavage of the arylalkyl ether system.

Catalytic hydrogenation of the unsaturated ketone (4) gave the saturated derivative (5; $R = CO_2Me$), in which the α-configuration at C-9 was assigned on the basis that the α-face of the precursor (4) would be the less hindered.[6] The next stage in our strategy involved *C*-methylation at C-13: but attempts to utilise various blocking groups [7] at C-11 to achieve this objective were unsuccessful. We therefore used the method of House *et al.*,[8] in which the enol acetate of a ketone is treated with methyl-lithium–methyl iodide. In preliminary experiments treatment of the ester (2; $R^1 = H$, $R^2 = CO_2Me$) with methyl-lithium gave a product in which the ketone (2; $R^1 = H$, $R^2 = COMe$) (τ 7.78) predominated.

To avoid this competitive conversion of the ester residue into the group $COCH_3$ and the probability of this reacting further during the vigorous conditions required for the methylation at C-13, the ketone (5; $R = CO_2Me$) was acetalised to give (7; $R = CO_2Me$): this was reduced with lithium aluminium hydride to the alcohol (7; $R = CH_2OH$). Removal of the blocking group with acid gave the ketone (5; $R = CH_2OH$), which was oxidised by chromic oxide to the oxo-acid (5; $R = CO_2H$). Enol acetylation of (5; $R = CH_2OH$) gave the diacetate (6; $R = CH_2OAc$), the identification of which

[3] W. P. Campbell and D. Todd, *J. Amer. Chem. Soc.*, 1940, **62**, 1287.

[4] R. H. Bible, jun., and R. R. Burtner, *J. Org. Chem.*, 1961, **26**, 1174.

[5] R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas, *J. Amer. Chem. Soc.*, 1955, **77**, 3230.

[6] R. E. Ireland and P. W. Schiess, *J. Org. Chem.*, 1963, **28**, 6.

[7] See *e.g.* W. S. Johnson, and H. Posvic, *J. Amer. Chem. Soc.*, 1947, **69**, 1361; R. E. Ireland and J. A. Marshall, *J. Org. Chem.*, 1962, **27**, 1615, 1620.

[8] H. O. House and V. Kramar, *J. Org. Chem.*, 1963, **28**, 3362; H. O. House and B. M. Trost, *ibid.*, 1965, **30**, 1341, 2502.

was in accord with spectral evidence (see Experimental section). Treatment of (6; R = CH_2OAc) with methyllithium followed by methyl iodide gave the 13α-methyl-12-ketone (8), together with the alcohol (5; R = CH_2OH), and the methyl ether (5; R = CH_2OMe). The conversion of (7; R = CH_2OAc) into (7; R = CH_2OMe) occurred under similar conditions. The structure (8) is in accord with the spectral data; although the stereochemical assignment is not unequivocal, we believe it reasonably well established on the basis of (i) general principles, since methylation will occur from the less hindered α-face, but more particularly (ii) n.m.r. evidence. Thus in solution in benzene axial methyl groups (and protons) are normally shielded, whereas equatorial methyl groups (and protons) experience either deshielding [9] or essentially no shift. The Δ value of −0.18 p.p.m. for the 13-methyl shift in benzene relative to the shift in deuteriochloroform indicated that the 13-methyl group is equatorial, and hence that 13-ethyl group is axial (and β) as required in the rosane system.[2]

In parallel with this part of the investigation we explored the construction of the 4,10-lactone–13β-methyl system of the rosane nucleus [2] by a route which is possibly biomimetic. Thus, deoxypodocarpic acid [10] (9) was reduced with t-pentyl alcohol–triethylamine–lithium to the dihydro-derivative (10), which was hydrogenated to the tetrahydro-derivative (11). This was readily converted into the γ-lactone (12), having the probable stereochemistry shown, in cold concentrated sulphuric acid (*cf.* ref. 11).

At this stage it seemed possible to develop this route for the synthesis of the rosane structure [type (1)]; but two factors intervened. First an elegant synthesis of rosenonolactone itself was reported,[12] and secondly it became clear that the technical difficulties of the reduction of (2; R^1 = Et, R^2 = CO_2H) to (3; R = H) were too great to justify the effort required to provide sufficient material for the completion of our objective. Consequently the project was discontinued.

EXPERIMENTAL

Unless indicated otherwise i.r. spectra were determined for Nujol mulls. Optical rotations were determined for solutions in methanol and u.v. spectra for solutions in ethanol.

Methyl 7-Ethyl-O-methylpodocarpate.—(*a*) Reduction of a solution of methyl 7-acetyl-*O*-methylpodocarpate (2.4 g) in methanol (25 ml) with sodium borohydride (0.75 g) during 8 h at room temperature gave *methyl 7-(1-hydroxyethyl)-O-methylpodocarpate* (1.8 g), which formed prisms, m.p. 150° [from light petroleum (b.p. 40—60 °C)]; $[\alpha]_D^{21}$ +93° (*c* 1.01); $\nu_{max.}$ 3 510 (OH) and 1 715 cm^{-1} (ester C=O) (Found: C, 73.1; H, 8.5. $C_{21}H_{30}O_4$ requires C, 72.8; H, 8.7%).

A solution of this alcohol (1 g) in tetrahydrofuran (20 ml) and liquid ammonia (250 ml) was reduced by addition of lithium (0.35 g). Isolated in the normal way, *methyl 7-ethyl-O-methylpodocarpate* (0.7 g) formed plates, m.p. 111—113° (from aqueous methanol); $[\alpha]_D^{22}$ +116° (*c* 1.21) (Found: C, 76.0; H, 9.2. $C_{21}H_{30}O_3$ requires C, 76.3; H, 9.2%).

(*b*) Reduction of methyl 7-acetyl-*O*-methylpodocarpate (62 g) by the Wolff–Kishner process, with diethylene glycol (400 ml), hydrazine hydrate (25 ml), and potassium hydroxide (12 g) at 120 °C during 2 h, followed by addition of further potassium hydroxide (28 g) before raising the temperature to 180 °C for 3 h, gave *7-ethyl-O-methylpodocarpic acid* (46.7 g), which formed needles, m.p. 183—184° [from acetone–light petroleum (b.p. 60—80 °C)]; $[\alpha]_D^{22}$ +132° (*c* 1.71) (Found: C, 75.8; H, 9.1. $C_{20}H_{28}O_3$ requires C, 75.9; H, 8.9%). Methylation with diazomethane gave the ester, identical with that from method (*a*).

(+)-*Methyl 7α-Ethyl-1α,4aβ-dimethyl-6-oxoperhydro(4bα,8aβ,10aαH)phenanthrene-1β-carboxylate* (5; R = CO_2Me).—A solution of 7-ethyl-*O*-methylpodocarpic acid (1 g) in t-pentyl alcohol (13 ml) and ethylamine (125 ml) was stirred *vigorously* with efficient cooling during the addition of lithium shot (0.85 g). After 45 min, the lithium had dissolved and the mixture was very pale blue in colour: more lithium (0.1 g) was added: *immediately* the first dark blue streaks appeared the reaction was quenched by the addition of t-pentyl alcohol. (These conditions are critical!) After evaporation of the ethylamine, water (25 ml) was added cautiously.

The combined products from *forty* such reductions were purified from aqueous methanol to yield (+)-*7-ethyl-6-methoxy-1α,4aβ-dimethyl-1,2,3,4,4a,5,8,9,10,10aα-decahydrophenanthrene-1β-carboxylic acid* (3; R = H) (22.1 g) in plates, m.p. 182—183°; $[\alpha]_D^{22}$ +128° (*c* 1.11); $\nu_{max.}$ 1 695 cm^{-1} (C=O of CO_2H); $\lambda_{max.}$ 273 (ε 890) and 280 nm (955); τ 6.47 (3 H, s, OCH_3), 8.72 (3 H, s, 1-Me), 9.03 (3 H, t, CH_2CH_3), and 9.07 (3 H, s, 4a-Me) [Found: C, 75.6; H, 9.4; OMe, 10.5. $C_{19}H_{27}O_2(OMe)$ requires C, 75.4; H, 9.5; OMe, 9.6%]. The action of diazomethane gave the (+)-*ester* (3; R = Me) (quantitatively) in prisms, m.p. 78—80° (from aqueous methanol); $[\alpha]_D^{22}$ +121° (*c* 1.70) (Found: C, 75.9; H, 9.5. $C_{21}H_{32}O_3$ requires C, 75.9; H, 9.7%).

The enolic methoxy-group of this ester was removed when a solution of the enol ether (8 g) in methanol (60 ml) containing water (2.8 ml) and 12N-hydrochloric acid (4 ml) was set aside during 1½ h. Purification of the product from aqueous methanol gave the (+)-*phenanthren-6-one* (4) (4 g) in needles, m.p. 162—165°; $[\alpha]_D^{22}$ +31.4° (*c* 1.15); $\nu_{max.}$ 1 720 (ester C=O), 1 660 (αβ-unsaturated C=O), and 1 605 cm^{-1} (C=C); $\lambda_{max.}$ 240 nm (log ε 3.17); τ 4.09 (1 H, d, vinylic, *J* 2 Hz), 6.31 (3 H, s, CO_2CH_3), 8.78 (3 H, s, 1-Me), 9.05 (3 H, s, 4a-Me), and 9.08 (3 H, t, *J* 7 Hz, CH_2CH_3) [Found: C, 75.3; H, 9.6; OMe, 9.8. $C_{19}H_{27}O_2(OMe)$ requires C, 75.4; H, 9.5; OMe, 9.8%].

Hydrogenation of a solution of the αβ-unsaturated ketone (1.6 g) in ethanol (200 ml) containing 10% palladium–charcoal (0.5 g) and 3N-hydrochloric acid (1 ml) was completed during 15 min, to give (+)-*methyl 7α-ethyl-1α,4aβ-dimethyl-6-oxoperhydro(4bα,8aβ,10aαH)phenanthrene-1β-carboxylate* (5; R = CO_2Me), which separated from light petroleum (b.p. 40—60 °C) in flat needles (1.2 g), m.p. 130°; $[\alpha]_D^{22}$ +49° (*c* 1.70); $\nu_{max.}$ 1 720 (ester C=O) and 1 700 cm^{-1} (six-

[9] J. Ronayne and D. H. Williams, *Chem. Comm.*, 1966, 712; N. S. Bhacca and D. H. Williams, *Tetrahedron Letters*, 1964, 3127.
[10] E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, 1958, **80**, 217.
[11] A. W. Burgstahler and L. R. Worden, *J. Amer. Chem. Soc.*, 1964, **86**, 96.
[12] T. McCreadie, K. H. Overton, and A. J. Allison, *J. Chem. Soc.* (*C*), 1971, 317.

membered ring C=O); τ 6.32 (3 H, s, CO_2CH_3), 8.81 (3 H, s, 1-Me), 9.13 (3 H, t, CH_2CH_3, *J* 7.0 Hz), and 9.27 (3 H, s, 4a-Me) [Found: C, 75.1; H, 10.2; OMe, 9.8. $C_{19}H_{29}O_2$(OMe) requires C, 75.0; H, 10.1; OMe, 9.7%].

Conversion of Methyl O-Methylpodocarpate into the 4β-(Methyl Ketone) (2; R^1 = H, R^2 = $COCH_3$).—A solution of the ester (0.1 g) in dimethoxyethane (2 ml) was added dropwise during 10 min at 0 °C (in nitrogen) to a solution of methyl-lithium in 1,2-dimethoxyethane (5 ml) containing triphenylmethane (5 mg). After 45 min at 0 °C the product was isolated and purified from light petroleum (b.p. 40—60 °C) to yield the *methyl ketone* (2; R^1 = H, R^2 = $COCH_3$) in plates (0.08 g), m.p. 120—122°; $\nu_{max.}$ (no ester peak) 1 690 cm^{-1} (ketone); τ 6.22 (3 H, s, OCH_3), 7.78 (3 H, s, $COCH_3$), 8.80 (3 H, s, 4-Me), and 8.95 (3 H, s, 10-Me) (Found: C, 79.6; H, 9.1. $C_{19}H_{26}O_2$ requires C, 79.7; H, 9.2%).

7α-Ethyl-1β-methoxymethylene-1α,4aβ-dimethylperhydro-(4bα,8aβ,10aαH)phenanthren-6-one (8).—A solution of the ketone (5; R = CO_2Me) (5 g) in ethylene glycol (150 ml) and benzene (300 ml) containing toluene-*p*-sulphonic acid (0.6 g) was refluxed during 24 h, with continuous removal of water. The (+)-*ethylene acetal* (7; R = CO_2Me) (4.3 g) separated from aqueous methanol in prisms, m.p. 110°; $[\alpha]_D^{22}$ +29° (*c* 1.83); $\nu_{max.}$ 1 720 cm^{-1} (ester C=O) (Found: C, 72.5; H, 10.1. $C_{22}H_{36}O_4$ requires C, 72.5; H, 10.0%).

Reduction of a solution of this acetal (4 g) in ether (150 ml) with lithium aluminium hydride (1 g) during 0.5 h, at room temperature (stir), gave the (+)-*alcohol* (7; R = CH_2OH) (3.5 g) in plates, m.p. 196° [from light petroleum (b.p. 40—60 °C)]; $[\alpha]_D^{23}$ +1.1° (*c* 1.03); $\nu_{max.}$ 3 510—3 475 cm^{-1} (OH) (Found: C, 74.8; H, 10.8. $C_{21}H_{36}O_3$ requires C, 75.0; H, 10.8%).

The *acetate* separated from aqueous methanol in prisms, m.p. 118°; $[\alpha]_D^{23}$ −2.9° (*c* 1.99); $\nu_{max.}$ 1 735 cm^{-1} (carbonyl of acetate) (Found: C,73.2; H, 10.5. $C_{23}H_{38}O_4$ requires C, 73.0; H, 10.1%).

Removal of the ethylene acetal residue from (7; R = CH_2OH) (3 g) during 2 h, on a steam-bath, with acetone (150 ml) and 3N-hydrochloric acid (10 ml), gave (+)-*7α-ethyl-1β-hydroxymethylene-1α,4aβ-dimethylperhydro*(4bα,-8aβ,10aαH)*phenanthren-6-one* (5; R = CH_2OH) (2.12 g), which formed needles, m.p. 66° [from light petroleum (b.p. 40—60 °C)]; $[\alpha]_D^{23}$ +20.5° (*c* 1.77); $\nu_{max.}$ 3 450—3 250 (OH) and 1 705 cm^{-1} (C=O) (Found: C, 77.7; H, 10.8. $C_{19}H_{32}O_2$ requires C, 78.0; H, 11.0%).

Oxidation of a solution of this alcohol (0.1 g) in acetic acid (5 ml) by addition of chromic oxide (0.1 g) in acetic acid (1 ml) gave (+)-*7α-ethyl-1α,4aβ-dimethylperhydro-(4bα,8aβ,10aαH)phenanthrene-1β-carboxylic acid* (5; R = CO_2H) (0.09 g) in fluffy needles, m.p. 159° (from aqueous methanol), $[\alpha]_D^{23}$ +45.4° (*c* 1.23); $\nu_{max.}$ 2 700—2 550 (OH), 1 705 (C=O), and 1 695 cm^{-1} (C=O) (Found: C, 74.8; H, 10.1. $C_{19}H_{30}O_3$ requires C, 74.5; H, 9.9%).

Acetylation of the ketol (5; R = CH_2OH) (0.75 g) in refluxing acetic anhydride (5 ml) containing toluene-*p*-sulphonic acid (0.3 g) with slow removal of acetic acid by distillation during 5 h gave the *enol acetate* (6; R = CH_2OAc) as a viscous oil, which was purified by chromatography on silica from light petroleum (b.p. 60—80 °C); τ 5.58 and 6.06 (2 H, dd, CH_2OAc), 8.18 (3 H, s, CH_3 of enol acetate), 8.25 (3 H, s, CH_3 of primary acetate), 9.00 (3 H, t, CH_2CH_3, *J* 7 Hz), 9.06 (3 H, s, 1-Me), and 9.32 (3 H, s, 4a-Me).

A solution of this enol acetate (0.4 g) in 1,2-dimethoxyethane (10 ml) was added slowly to a solution of methyl-lithium (5 equiv.) in the same solvent (40 ml) containing triphenylmethane (5 mg); 45 min later at 0 °C methyl iodide (3 ml) was added. The mixture was stirred at 40 °C for 0.5 h, and then decomposed by addition of 2N-hydrochloric acid. On isolation, the crude product was purified by chromatography on alumina from light petroleum (b.p. 40—60 °C)–ether (19 : 1) to give the (+)-*ketone* (8) (0.1 g), which formed plates, m.p. 82—84° (from aqueous methanol); $[\alpha]_D^{22}$ +92° (*c* 1.03); $\nu_{max.}$ (CCl_4) 1 698 cm^{-1} (C=O); τ 6.68 and 6.92 (2 H, dd, CH_2OCH_3, *J* 9 Hz), 6.76 (3 H, s, CH_2OCH_3), 9.05 (3 H, t, CH_2CH_3, *J* 9 Hz), 9.10 (3 H, s, 1-Me), and 9.23 (3 H, s, 4a-Me) [Found: C, 78.8; H, 11.5; OMe, 10.0. $C_{20}H_{33}O$(OMe) requires C, 78.7; H, 11.3; OMe, 9.7%].

When the acetate (7; R = CH_2OAc) (0.1 g) was treated with methyl-lithium (3 equiv.) as in the previous experiment, *7α-ethyl-1β-methoxymethylene-1α,4aβ-dimethylperhydro(4bα,8aβ,10aαH)phenanthren-6-one* (5; R = CH_2OMe) (0.05 g) was produced as needles, m.p. 47—48° (from aqueous methanol); $\nu_{max.}$(CCl_4) 1 710 cm^{-1} (C=O) (Found: C, 78.0; H, 11.0. $C_{20}H_{34}O_2$ requires C, 78.4; H, 11.2%).

Lactonisation of the Unsaturated Acid (11).—A solution of deoxypodocarpic acid (0.33 g) in t-pentyl alcohol (5 ml) and ethylamine (75 ml) was added with vigorous stirring to finely divided lithium (0.35 g). After 1 h the lithium had dissolved and the mixture was pale bluish in colour. More lithium (0.1 g) was then introduced; *immediately* the first dark blue streaks appeared, t-pentyl alcohol was added to quench the reaction. After isolation with ether the product was purified from aqueous methanol and then from light petroleum (b.p. 40—60 °C) to yield (+)-*1α,4aβ-dimethyl-1,2,3,4,4a,5,8,9,10,10aα-decahydrophenanthrene-1β-carboxylic acid* (10) (0.31 g) in prisms, m.p. 165—167°; $[\alpha]_D^{23}$ +159° (*c* 0.71) (Found: C, 78.2; H, 9.4. $C_{17}H_{24}O_2$ requires C, 78.4; H, 9.3%).

Hydrogenation of this phenanthrene (0.2 g) in ethanol (15 ml) over platinum oxide (0.2 g) during 45 min gave the *6,7-dihydro-derivative* (11), which formed prisms (0.2 g), m.p. 146° (from aqueous methanol); $[\alpha]_D^{23}$ +184° (*c* 0.53) (Found: C, 77.9; H, 9.8. $C_{17}H_{26}O_2$ requires C, 77.8; H, 10.0%).

This acid (0.1 g) was added slowly to stirred concentrated sulphuric acid (3 ml) at −10 °C; 50 min later the solution was poured onto ice and the product extracted with ether. Purification from aqueous methanol gave (+)-*1α,4bβ-dimethylperhydro(10aαH)phenanthrene-1β,4aβ-carbolactone* (12) (0.05 g) in needles, m.p. 81° (from aqueous methanol); $[\alpha]_D^{22}$ +29° (*c* 0.93); $\nu_{max.}$ 1 750 cm^{-1} (γ-lactone) (Found: C, 78.0; H, 10.1. $C_{17}H_{26}O_2$ requires C, 77.8; H, 10.0%).

We thank the Nuffield Foundation for financial assistance.

[7/1250 *Received*, 13*th July*, 1977]