Naturally Occurring Dibenzofurans. Part 7.[1] The Synthesis of ψ-Rhodomyrtoxin

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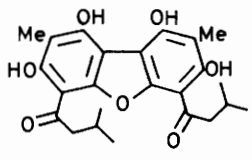
The synthesis of 1,1'-(1,3,7,9-tetrahydroxy-2,8-dimethyldibenzofuran-4,6-diyl)-2,3'-dimethylbisbutan-1-one (ψ-rhodomyrtoxin) (**2**) is described. Intramolecular Ullmann reaction of bis(2-iodo-3,5-dimethoxy-4-methylphenyl) ether (**8**) yielded 1,3,7,9-tetramethoxy-2,8-dimethyldibenzofuran (**9**) which was converted, in subsequent steps, into the natural product.

In a previous paper[2] we adduced evidence in favour of structures (**1**) and (**2**) for rhodomyrtoxin[3] and ψ-rhodomyrtoxin,[4] respectively, compounds which were isolated from the fruit of the Australian finger cherry, *Rhodomyrtus macrocarpa* Benth. However, we have been unable to obtain a supply of the fruit, and although ψ-rhodomyrtoxin and its derivatives are available,[5] the samples of rhodomyrtoxin and its derivatives were no longer extant[5,6] and the spectroscopic data reported[3] for these compounds are meagre. We have therefore confined further synthetic work to ψ-rhodomyrtoxin.

In order to synthesise compound (**2**), the most plausible structure for ψ-rhodomyrtoxin, it was necessary to devise an efficient synthesis of the dibenzofuran (**9**) (see Scheme). A number of previous attempts had met with failure,[2,7] but the solution to the problem was found in the intramolecular Ullmann reaction of the bis(iodophenyl) ether (**8**), readily available by iodination of the known diphenyl ether (**7**).[2] When the former compound was heated with activated copper bronze under dry nitrogen the dibenzofuran (**9**) was obtained in 88% yield. Ollis and his co-workers had claimed to obtain this symmetrical dibenzofuran both by synthesis and by degradation of ψ-rhodomyrtoxin.[4] As expected our synthetic product was different from the dibenzofuran obtained by Ollis and his co-workers, the structure of which we had previously revised to the alternative symmetrical dibenzofuran (**3**).[2]

The synthesis of compound (**2**) was now unexceptional. Isovalerylation of the dibenzofuran (**9**) with an excess of isovaleryl chloride in the presence of tin (IV) chloride in dichloromethane solution at room temperature during 16 h gave a mixture of two products. The minor product (17%) proved to be the expected ketone (**10**). The major product (74%) was a demethylation product of the expected ketone as shown by its mass spectrum and its elemental analytical data and those of the derived acetate. The i.r. spectrum of the hydroxyketone exhibited bands assigned to a bonded hydroxy group at 3 350 cm^{-1} and to a non-bonded ketone at 1 695 cm^{-1}. The sharp hydroxy proton resonance in the ^1H n.m.r. spectrum of the hydroxyketone occurred at δ 9.08, a value consistent with a 9-methoxydibenzofuran-1-ol.[2] Since the ^1H n.m.r. chemical shift of the aromatic proton of the hydroxyketone only changed by 0.05 p.p.m. on acetylation, the hydroxy group cannot occupy a free *para*-position[8] and structure (**11**) is thus proposed. Further evidence for structure (**11**) was adduced by brief treatment of the hydroxyketone with boron trichloride when selective demethylation of the methoxy group *ortho* to the carbonyl group occurred and compound (**12**) resulted. In keeping with this structure the i.r. spectrum of this compound exhibited a band at 1 600 cm^{-1} assigned to a bonded ketone and the n.m.r. spectrum now showed two sharp hydroxy proton resonances at δ 9.40 (1-OH) and 13.90 (3-OH). Presumably the hydroxyketone (**11**) arises by Lewis acid induced demethylation of the most hindered methoxy group in the ketone (**10**). The



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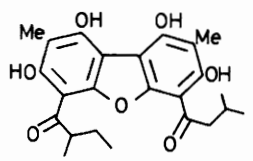

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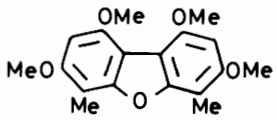

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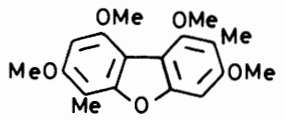

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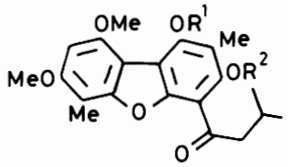
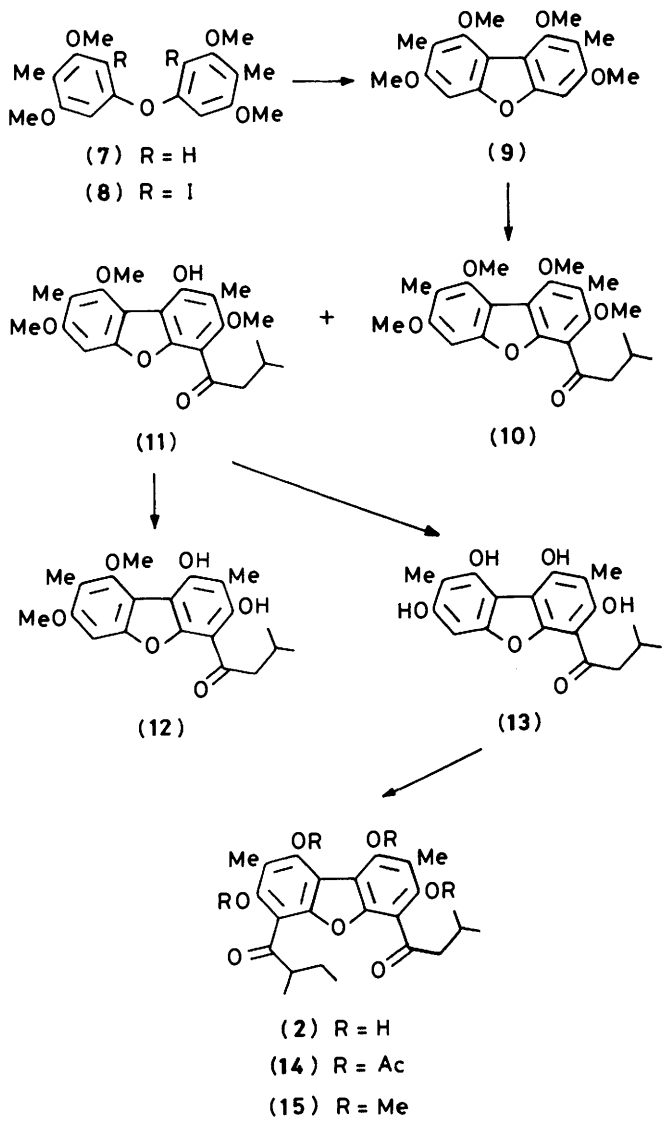


(5) R^1 = Me, R^2 = H
(6) R^1 = H, R^2 = Me

results of a more detailed study of this type of reaction are reported in a preliminary communication.[9]

During our previous work[2] we encountered a similar example of demethylation during the isovalerylation of the dibenzofuran (**4**). We erroneously assigned structure (**5**) to the product which is now amended to structure (**6**). In agreement with this structure the i.r. spectrum (CCl_4) of the compound exhibits bands at 3 400 cm^{-1} (bonded OH) and at 1 698 cm^{-1} (non-bonded ketone).

Treatment of the hydroxyketone (**11**) with boron tribromide effected complete demethylation and supplied the tetraol (**13**) which was characterised as the derived tetra-acetate. The tetraol (**13**) was allowed to react with 2-methylbutyric acid in the presence of boron trifluoride–diethyl ether and the crude product was acetylated, thus affording compound (**14**). Mild hydrolysis of the tetra-acetate (**14**) then gave synthetic ψ-rhodomyrtoxin (**2**), also characterised as its tetra-*O*-methyl ether (**15**). Unfortunately we have been unable to make direct comparisons between synthetic ψ-rhodomyrtoxin (**2**), its tetra-acetate (**14**), and its tetra-*O*-methyl ether (**15**) and the relevant authentic materials. However, the ^1H n.m.r. spectral data for the synthetic compounds agree closely with those reported for the natural compounds.[4] The m.p.s of synthetic ψ-rhodomyrtoxin



Scheme.

and its tetra-*O*-methyl ether are also very close to the literature values, but the m.p. of the synthetic tetra-acetate is 34 °C higher than that recorded for the natural material, for which, however, no elemental analytical data are reported.[4] We believe that the present work provides very strong evidence for structure (**2**) for ψ-rhodomyrtoxin.

Experimental

General directions are given in Part 4.[7]

Bis(3,5-*dimethoxy*-4-*methylphenyl*) *Ether* (**7**).—This compound was prepared by the method of Sargent *et al.*[2] The intermediate 6-(2,5-*dimethoxy*-4-*methylphenoxy*)-2,4-*dimethoxy*-3-*methylbenzoic acid* formed feathery needles (from dichloromethane–light petroleum), m.p. 142.5—144.5 °C (Found: C, 63.0; H, 6.15%; M^+, 362. $C_{19}H_{22}O_6$ requires C, 62.95; H, 6.1%; *M*, 362); δ 2.04 and 2.11 (each 3 H, s, Me), 3.67 (3 H, s, OMe), 3.73 (6 H, s, 2 × OMe), 3.84 (3 H, s, OMe), 6.24—6.27 (3 H, m, ArH), and 8.99 (1 H, br, OH).

Bis(2-*iodo*-3,5-*dimethoxy*-4-*methylphenyl*) *Ether* (**8**).—A solution of iodine (2.06 g) in chloroform (50 ml) was added dropwise during 30 min to a stirred solution of the diphenyl ether (**7**) (1.23 g) in chloroform (20 ml) containing suspended silver trifluoroacetate (1.80 g). The suspension was stirred for a further 10 min and then filtered through a pad of Celite which was washed with a little chloroform. The filtrate was washed in turn with water, dilute sodium thiosulphate solution, water, and finally with saturated brine. The residue left on removal of the solvent crystallized from light petroleum as plates of the *di-iodo compound* (**8**) (2.13 g, 97%), m.p. 123.5—124.5 °C (Found: C, 38.15; H, 3.55; I, 44.6%; M^+, 570. $C_{18}H_{20}I_2O_5$ requires C, 37.9; H, 3.55; I, 44.5%; *M*, 570); δ 2.17 (6 H, s, 2 × Me), 3.56 and 3.77 (each 6 H, s, 2 × OMe), and 6.20 (2 H, s, ArH).

1,3,7,9-*Tetramethoxy*-2,8-*dimethyldibenzofuran* (**9**).—An intimate mixture of the iodo compound (**8**) (560 mg) and activated copper bronze (560 mg) was covered with a thin layer of copper bronze and heated at 200 °C (bath) under dry nitrogen for 0.5 h. The mixture was then heated for 1 h longer at 260 °C (bath). The cooled mixture was exhaustively extracted with boiling acetone and the acetone was then removed by distillation under reduced pressure. The residue was dissolved in ethyl acetate and washed in turn with dilute sodium thiosulphate solution, water, and finally with saturated brine. The crude product was filtered through a plug of alumina with 2% ethyl acetate–light petroleum as eluant. The *dibenzofuran* (**9**) (273 mg, 88%) formed plates (from methanol), m.p. 149—151 °C (Found: C, 68.8; H, 6.55%; M^+, 316. $C_{18}H_{20}O_5$ requires C, 68.35; H, 6.35%; *M*, 316); δ 2.57 (6 H, s, 2 × Me), 3.87 and 3.88 (each 6 H, s, 2 × OMe), and 6.82 (2 H, s, ArH); $\lambda_{max.}$(EtOH) 227, 263, and 299 nm (ε 39 400, 13 500, and 18 400).

Isovalerylation of 1,3,7,9-*Tetramethoxy*-2,8-*dimethyldibenzofuran* (**9**).—A solution of tin(IV) chloride (4.11 g) in anhydrous dichloromethane (15 ml) was added dropwise under dry nitrogen at 0 °C to a solution of the dibenzofuran (**9**) (1.00 g) and isovaleryl chloride (1.91 g) in anhydrous dichloromethane (15 ml). The solution was then stirred at room temperature for 16 h and then poured into cold aqueous sodium hydrogen carbonate. Isolation with ethyl acetate in the usual way gave the crude product which was subjected to flash chromatography over silica with 5% ethyl acetate–light petroleum as eluant. The first band which was eluted gave 1-(1,3,7,9-*tetramethoxy*-2,8-*dimethyldibenzofuran*-4-*yl*)-3-*methylbutanone* (**10**) (210 mg, 17%) which formed needles (from methanol), m.p. 92—93 °C (Found: C, 68.7; H, 7.25%; M^+, 400. $C_{23}H_{28}O_6$ requires C, 69.0; H, 7.05%; *M*, 400); δ 1.02 (6 H, d, *J* 7.0 Hz, $CHMe_2$), 2.26 and 2.34 (each 3 H, s, 2- and 8-Me), 2.34 (1 H, m, $CHMe_2$), 2.96 (2 H, d, *J* 7.0 Hz, $COCH_2$), 3.82, 3.86, 3.87, and 3.89 (each 3 H, s, OMe), and 6.90 (1 H, s, ArH); irradiation at δ 1.02 caused collapse of the $CHMe_2$ signal to a triplet, and irradiation at δ 2.34 caused collapse of the $CHMe_2$ and the $COCH_2$ signals to singlets; $\lambda_{max.}$(EtOH) 219, 264, and 295 nm (ε 86 900, 50 300, and 2 000). Further elution afforded 1-(1-*hydroxy*-3,7,9-*trimethoxy*-2,8-*dimethyldibenzofuran*-4-*yl*)-3-*methylbutan*-1-*one* (**11**) (900 mg, 74%) which formed needles (from methanol), m.p. 88—90 °C (Found: C, 69.05; H, 7.1. $C_{22}H_{26}O_6$ requires C, 68.35; H, 6.8%); δ 1.01 (6 H, d, *J* 7.0 Hz, $CHMe_2$), 2.23 and 2.27 (each 3 H, s, ArMe), 2.27 (1 H, m, $CHMe_2$), 2.97 (2 H, d, *J* 7.0 Hz, $COCH_2$), 3.82, 3.87, and 3.96 (each 3 H, s, OMe), 6.92 (1 H, s, ArH), and 9.08 (1 H, s, OH); $\nu_{max.}$(CCl_4) 3 350 (bonded OH) and 1 695 cm^{-1} (free CO); $\lambda_{max.}$(EtOH) 216, 265, 283, and 304 infl. nm (ε 42 500, 31 500, 23 400, and 16 700); *m/z* 386 (M^+, 39%), 330 (24), 329 (100), 314 (26), 302 (19), and 271 (13). The *acetate* formed fine needles (from dichloromethane–light petroleum), m.p. 144.5—145.5 °C (Found: C, 67.55; H, 6.65. $C_{24}H_{28}O_7$ requires C, 67.3; H, 6.6%); δ 1.03 (6 H, d, *J* 6.5 Hz, $CHMe_2$), 2.21, 2.23, and 2.45 (each 3 H, s, 2 × Me and COMe), 2.99 (2 H, d, *J* 7.0 Hz, $COCH_2$), 3.79, 3.81, and 3.85 (each 3 H, s, OMe), and

6.87 (1 H, s, ArH); the C*H*Me$_2$ signal was obscured by the signal at δ 2.23.

1-(1,3-*Dihydroxy*-7,9-*dimethoxy*-2,8-*dimethyldibenzofuran*-4-*yl*)-3-*methylbutan*-1-*one* (**12**).—A solution of boron trichloride (250 mg) in anhydrous dichloromethane (2 ml) was added dropwise at −10 °C to a stirred solution of the phenol (**11**) (250 mg) in anhydrous dichloromethane (10 ml). After 1.75 h water was added and the mixture was extracted with ethyl acetate. The extract was washed in turn with water, saturated sodium hydrogen carbonate solution, and finally with saturated brine. The crude product crystallized from light petroleum as fine yellow needles (210 mg, 87%) of the *diol* (**12**), m.p. 147.5—150.5 °C (Found: C, 67.25; H, 6.8. $C_{21}H_{24}O_6$ requires C, 67.75; H, 6.5%); δ 1.07 (6 H, d, *J* 6.5 Hz, C*H*Me$_2$), 2.16 and 2.24 (each 3 H, s, ArMe), 2.31 (1 H, m, C*H*Me$_2$), 3.08 (2 H, d, *J* 7.0 Hz, COC*H*$_2$), 3.90 and 3.95 (each 3 H, s, OMe), 6.82 (1 H, s, ArH), and 9.40 and 13.91 (each 1 H, s, 1-OH and 3-OH, both exchangeable with D_2O); $\nu_{max.}$(CHCl$_3$) 3 220 (OH), 2 850 (OH), and 1 600 cm^{-1} (bonded CO); $\lambda_{max.}$(EtOH) 220, 262 infl., 269, 290, and 351 nm (ε 30 100, 25 900, 31 500, 25 300, and 3 500).

1-(1,3,7,9-*Tetrahydroxy*-2,8-*dimethyldibenzofuran*-4-*yl*)-3-*methylbutan*-1-*one* (**13**).—A solution of boron tribromide (697 mg) in anhydrous dichloromethane (8.7 ml) was added dropwise to a stirred solution of the phenol (162.5 mg) in anhydrous dichloromethane (3.0 ml) at −10 °C under dry nitrogen. The dark red solution gradually faded to orange and after 2 h it was poured into water and extracted with ethyl acetate. The extract was washed in turn with water, saturated sodium hydrogen carbonate solution, water, and finally with saturated brine. Removal of the solvent gave the tetraol (**13**) (139 mg, 96%) as a pale orange powder, m.p. >315 °C; δ 1.05 (6 H, d, *J* 6.5 Hz, CH*Me*$_2$), 2.13 and 2.18 (each 3 H, s, ArMe), 2.23 (1 H, m, C*H*Me$_2$), 3.08 (2 H, d, *J* 6.7 Hz, CH$_2$CO), 6.34—7.39 (3 H, vbr, OH), 6.71 (1 H, s, ArH), and 13.88 (1 H, s, OH). The *tetra-acetate* formed prisms (from dichloromethane–light petroleum), m.p. 194.5—196.5 °C (Found: C, 63.6; H, 5.65. $C_{27}H_{28}O_{10}$ requires C, 63.3; H, 5.5%); δ (80 MHz) 1.01 (6 H, d, *J* 6.5 Hz, CH*Me*$_2$), 2.09 (6 H, s, 2 × COMe), 2.35 and 2.37 (each 3 H, s, ArMe), 2.43 and 2.45 (each 3 H, s, 2 × COMe), 3.03 (2 H, d, *J* 6.9 Hz, COCH$_2$), and 7.32 (1 H, s, ArH); the C*H*Me$_2$ resonance was obscured by the acetate resonances.

1,1′-(1,3,7,9-*Tetrahydroxy*-2,8-*dimethyldibenzofuran*-4,6-*diyl*)-2,3′-*dimethylbisbutan*-1-*one* (ψ-*Rhodomyrtoxin*) (**2**).—A solution of the tetraol (**13**) (250.6 mg) in 2-methylbutyric acid (3.0 ml) and boron trifluoride–diethyl etherate (3.0 ml) was stirred and heated at 95—100 °C (bath) under dry nitrogen for 6 h. The solution was then cooled and diluted with ethyl acetate and washed successively with saturated sodium hydrogen carbonate solution, water, and finally with saturated brine. The residue was then boiled under reflux under dry nitrogen with ethanol (20 ml) for 4 h. The crude product was then acetylated (acetic anhydride, pyridine, room temperature, 20 days) in the usual way. Flash chromatography of the crude product over silica with 20% ethyl acetate–light petroleum as eluant gave ψ-*rhodomyrtoxin tetra-acetate* (**14**) (271 mg, 62%) which formed prisms (from aqueous methanol), m.p. 152—153 °C (lit.,[4] m.p. 118—119 °C) (Found: C, 64.65; H, 6.2. $C_{32}H_{36}O_{11}$ requires C, 64.45; H, 6.1%); δ 0.92 (3 H, t, *J* 6.7 Hz, CH$_2$*Me*), 0.98 (6 H, d, *J* 6.7 Hz, CH*Me*$_2$), 1.21 [3 H, d, *J* 7.0 Hz, CH(*Me*)Et], 1.38—2.20 [3 H, m, COCH$_2$C*H*Me$_2$ and COCH(Me)C*H*$_2$Me], 2.10 (6 H, s, 2 × COMe), 2.33 and 2.35 (each 3 H, s, ArMe), 2.46 (6 H, s, 2 × COMe), 2.99 (2 H, d, *J* 7.0 Hz, COC*H*$_2$CHMe$_2$), and 3.33—3.57 [1 H, m, COC*H*(Me)Et]; $\nu_{max.}$(CHCl$_3$) 1 750, 1 680, and 1 600 cm^{-1}; $\lambda_{max.}$(EtOH) 239, 246infl., 257infl., and 300 nm (ε 28 700, 27 200, 23 000, and 16 400); *m*/*z* 596 (*M*$^+$, 22%), 554 (30), 512 (93), 470 (27), 428 (100), 371 (53), and 343 (7). The tetra-acetate (**14**) (224 mg) was stirred in methanol (10 ml) and aqueous sodium hydroxide (10 ml, 10%) under nitrogen for 1.5 h at room temperature. Acidification and isolation with ethyl acetate gave ψ-rhodomyrtoxin (**2**) (155 mg, 96%) which was crystallised from aqueous methanol and then sublimed at 158 °C at 0.01 mmHg, whereupon it was obtained as yellow needles, m.p. 203—205 °C (lit.,[4] 201 °C); δ (80 MHz) 0.92 (3 H, t, *J* 7.4 Hz, CH$_2$*Me*), 1.07 (6 H, d, *J* 6.9 Hz, CH*Me*$_2$), 1.31 [3 H, d, *J* 6.9 Hz, CH(*Me*)Et], 1.42—2.73 [3 H, m, COCH$_2$C*H*Me$_2$ and COCH(Me)C*H*$_2$Me], 2.23 (6 H, s, 2 × ArMe), 3.22 (2 H, d, *J* 6.3 Hz, COC*H*$_2$CHMe$_2$), 3.95—4.37 [1 H, m, COC*H*(Me)Et], 4.25—7.16 (2 H, OH), and 13.98 and 14.27 (each 1 H, s, OH); $\nu_{max.}$(KBr), 3 300, 2 970, and 1 615 cm^{-1}; $\lambda_{max.}$(EtOH) 223infl., 266, 293, and 356 nm (ε 17 100, 38 900, 23 700, and 7 300); *m*/*z* 428 (*M*$^+$, 100%) and 371 (71). The *tetra*-O-*methyl ether* (**15**) (methyl iodide, potassium carbonate, and dimethylformamide under dry nitrogen) formed laths (from aqueous methanol), m.p. 142—144.5 °C (lit.,[4] 137—139 °C) (Found: C, 69.45; H, 7.5. $C_{28}H_{36}O_7$ requires C, 69.4; H, 7.5%); δ 0.96 (3 H, t, *J* 7.7 Hz, CH$_2$*Me*), 1.00 (6 H, d, *J* 6.7 Hz, CH*Me*$_2$), 1.21 [3 H, d, *J* 7.2 Hz, CH(*Me*)Et], 1.31—2.42 [3 H, m, COC*H*Me$_2$ and COCH(Me)-C*H*$_2$Me], 2.35 (6 H, s, 2 × ArMe), 2.92 (2 H, d, *J* 7.0 Hz, COC*H*$_2$CHMe$_2$), 3.17—3.41 [1 H, m, COC*H*(Me)Et], 3.82 and 3.83 (each 3 H, s, OMe), and 3.89 (6 H, s, 2 × OMe); $\nu_{max.}$(KBr) 1 695 and 1 590 cm^{-1}; $\lambda_{max.}$(EtOH) 217, 251, 262infl., and 296infl. (ε 39 000, 26 400, 22 300, and 13 500); *m*/*z* 484 (*M*$^+$, 19%), 428 (24), and 427 (100).

Acknowledgements

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