Basic Intramolecular Acylation. Synthesis of 2-Aryl-1-tetralones bearing Isopropoxy or Benzyloxy Groups, Synthetic Key Intermediates for Phenolic Antileukaemic Benzo[*c*]phenanthridine Alkaloids, from 2,4-Diarylbutyric Acid Derivatives†[1]

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Generally applicable intramolecular cyclisation of 2,4-diarylbutyric acids having isopropoxy (**4**) or benzyloxy (**12**) groups used to protect phenolic functions was required for the purpose of synthesis of phenolic benzo[*c*]phenanthridine alkaloids. Treatment of the butyric acids (**4b**), (**4d**), (**4f**), and (**12**) with $POCl_3$ in acetonitrile in the presence of potassium carbonate furnished the corresponding tetralones (**5b**), (**5d**), (**5f**), and (**13**) in excellent yield, respectively, without the cleavage of its isopropoxy or benzyloxy groups. A plausible mechanism for basic intramolecular acylation using $POCl_3$ is proposed.

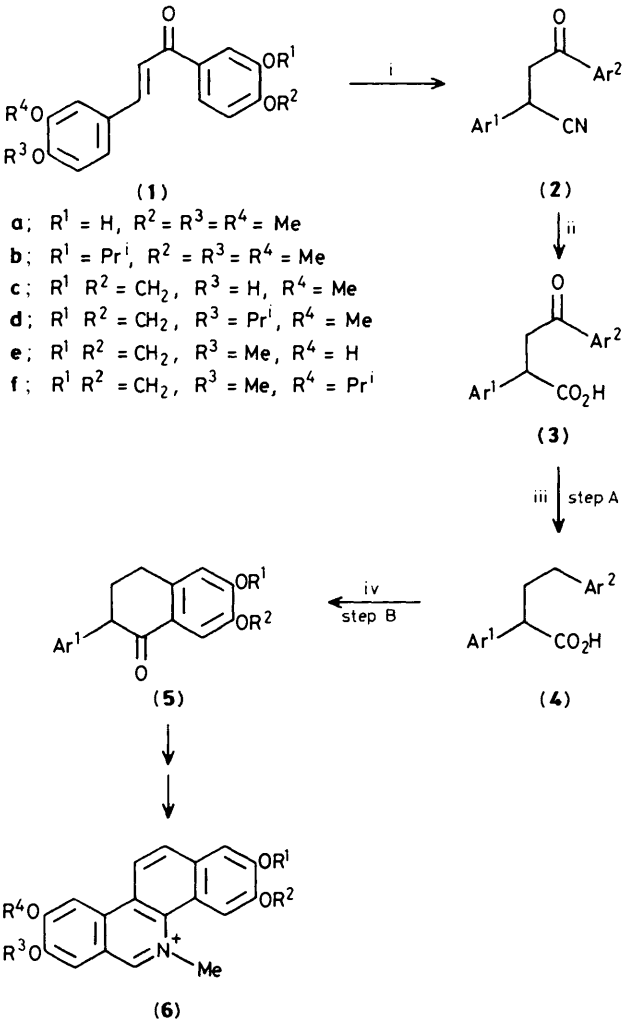
In previous papers,[2] we reported the widely applicable synthetic method for cytotoxic,[2b] fully aromatised, nonphenolic, quaternary benzo[*c*]phenanthridine alkaloids[3] (**6**) shown in Scheme 1. However, the synthetic sequence was not directly applicable to the synthesis of phenolic alkaloids, because the common groups used to protect phenolic functions, such as benzyloxy and methoxymethyl groups, would be cleaved in the hydrogenolysis of 2,4-diaryl-4-oxobutyric acids (**3**) by catalytic hydrogenation to 2,4-diarylbutyric acids (**4**) (step A) and/or in the intramolecular cyclisation of the resulting butyric acids (**4**) with phosphoryl trichloride ($POCl_3$) in chloroform to 2-aryl-1-tetralones (**5**) (step B).

Recently, we[1,4] succeeded in applying our method to the synthesis of fagaronine (**6a**), a phenolic antileukaemic alkaloid, using an isopropoxy group for protection. In this experiment, treatment of the isopropoxy acid (**4b**) with $POCl_3$ in chloroform provided the desired nonphenolic tetralone (**5b**) in relatively good yield, although a small amount of the free phenol by-product (**5a**) was produced by cleavage of the isopropoxy group.

On the other hand, in the course of our studies on the chemical constituents of Rutaceous plants, we[5] occasionally isolated a new phenolic oxybase (benzo[*c*]phenanthridone alkaloid) designated as oxyterihanine (**7a**) from Formosan *Xanthoxylum nitidum* (Roxb.) D.C. (*Fagara nitida* Roxb.) (Japanese name, Teriha-zansho). Unfortunately, the isolated amount of the alkaloid was so small that the choice of structure between two possible formulae (**7a**) and (**7b**) having a phenolic group at the C-8 and the C-9 positions remained to be solved. Thus, we undertook to prepare these two compounds for direct comparison with a sample of naturally occurring oxyterihanine.

O-Isopropylvanillin (**8a**) and *O*-isopropylisovanillin[1,4] (**8b**) were treated with acetopiperone (**9**) and sodium hydroxide in ethanol to give the starting chalcones (**1d**) and (**1f**) in 89.1 and 94.0% yield, respectively. These chalcones were converted into the corresponding acids (**4d**) and (**4f**) according to our synthetic sequence[1,6] in excellent yield. However, treatment of both acids (**4d**) and (**4f**) with $POCl_3$ in chloroform provided unsatisfactory results. In particular, the 4-isopropoxy acid (**4d**) gave a phenolic mixture (in 19.5% yield) showing four spots on t.l.c., though, in the case of fagaronine (**6a**), the same treatment of the corresponding acid (**4b**) gave the desired nonphenolic tetralone (**5b**) in reasonable yield. This situation forced us to find better conditions for intramolecular acylation of the acids (**4**) to the tetralones (**5**).

Initially, we tried to cyclise the acid (**4**) with $POCl_3$ in the absence of hydrogen chloroide formed during the reaction.



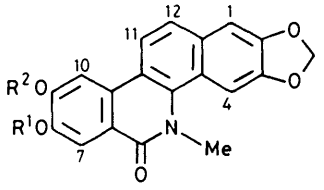
Scheme 1. *Reagents:* i, KCN–AcOH–$EtOCH_2CH_2OH$; ii, NaOH–EtOH; iii, H_2–Pd–C–AcOH; iv, $POCl_3$–$CHCl_3$

† This paper forms Part 63 of 'Studies on the Chemical Constituents of Rutaceous Plants,' by H. Ishii.

Table 1. Yields of the tetralone (**5d**) from the acid (**4d**) with various molar equivalents of phosphoryl trichloride ($POCl_3$) in chloroform in the presence of potassium carbonate[a]

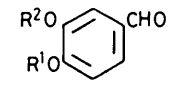
$POCl_3$ (mol equiv.)	3.5	4.6	5.4	6.5	7.5
(**5d**) (yield %)	59.4	76.1	78.2	82.1	86.2

[a] Conditions: acid (**4d**)–K_2CO_3–$CHCl_3$ = 5 g–20 g–25 ml; reflux for 70 min.



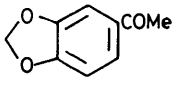
(**7**)

a; R^1 = H, R^2 = Me
b; R^1 = Me, R^2 = H



(**8**)

a; R^1 = Pr^i, R^2 = Me
b; R^1 = Me, R^2 = Pr^i



(**9**)

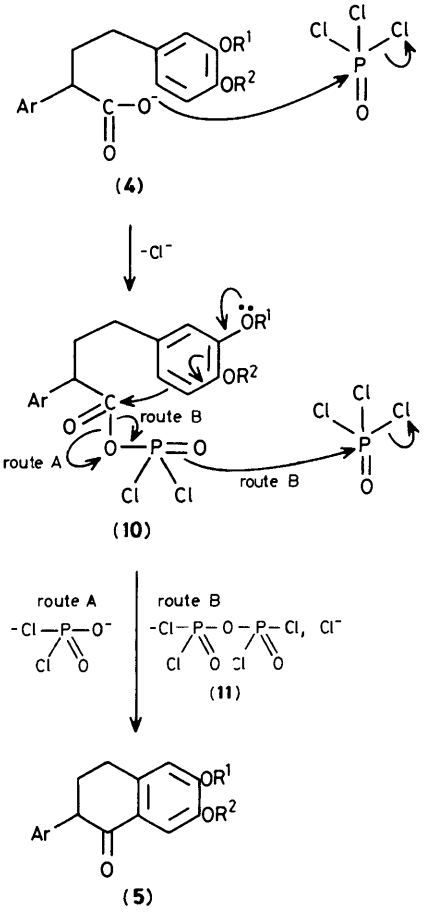
Thus, a 20% (g ml^{-1}) solution of the 4-isopropoxy acid (**4d**) in chloroform was treated with some definite increment of $POCl_3$ in the presence of a large amount of potassium carbonate (20 mol equiv.). In these experiments, the desired nonphenolic tetralone (**5d**) was obtained without formation of the phenolic by-product (**5c**), and its yield increased with increasing amount of $POCl_3$ as shown in Table 1. Moreover, the formation of minute amounts of an acid anhydride and of an ethyl ester of the starting acid (**4d**) as by-products was recognised by spectral inspection of the crude reaction mixture. The ester was believed to be produced from ethanol present in chloroform as a stabilising agent. These experimental results show distinctly that an excess of $POCl_3$ was favourable for completion of the reaction.

This conclusion can be explained by supposing that the first molecule of $POCl_3$ reacts with the starting acid (**4**) to give a mixed anhydride (**10**). The second molecule of $POCl_3$ attacks the resulting mixed anhydride (**10**) to give the desired tetralone (**5**) and dichlorophosphoric anhydride [$Cl_2P(O)OP(O)Cl_2$] (**11**). In other words, $POCl_3$ does not act as a reagent for formation of an acid chloride of the acid (**4**) but as a reagent providing the mixed anhydride (**10**) and cyclising this resulting mixed anhydride. This deduction led us to conclude that 2 mol equiv., at least, of $POCl_3$ are required for the cyclisation (Scheme 2).

Subsequently, we tried to find the optimum conditions for the basic cyclisation. In order to investigate the effects of choice of solvent, the 4-isopropoxy acid (**4d**) was treated with $POCl_3$ in various solvents [benzene, nitrobenzene, carbon tetrachloride, dimethyl sulphoxide (DMSO), or $POCl_3$ itself] to give the desired tetralone (**5d**) only in unsatisfactory yield, as shown in Table 2. However, treatment of a 14.7% (g ml^{-1}) solution of the 4-isopropoxy acid (**4d**) in acetonitrile with $POCl_3$ (5.0 mol equiv.) gave the desired tetralone (**5d**) in 91.3% yield without formation of the phenolic by-product (**5c**). Under the same conditions the 3-isopropoxy acid (**4f**) gave the desired tetralone (**5f**) in 78.1% yield also without formation of the phenolic by-

Table 2. Yields of the tetralone (**5d**) from the acid (**4d**) depending on solvents used

Solvent	(**4d**)/Solvent (g ml^{-1})	K_2CO_3 (mol equiv.)	$POCl_3$ (mol equiv.)	Conditions (°C/h)	Yield (%)
PhH	0.2	10.8	7.5	reflux/2	41.6
$PhNO_2$	0.2	1.1	10.0	60/1	< 51.6
CCl_4	0.2	1.1	10.0	60/7	71.9
DMSO	0.2	2.2	5.0	60/1.5	
Neat		1.0	10.0	reflux/1.5	65.2
MeCN	0.15	2.2	5.0	60/2.5	91.3



Scheme 2.

product (**5e**). In addition, in order to find a homogeneous reaction system, a solution of the 4-isopropoxy acid (**4d**) and $POCl_3$ in acetonitrile containing triethylamine was refluxed. However, this trial resulted in formation of only a complex mixture showing many spots on t.l.c. but without any indication of the desired tetralone (**5d**).

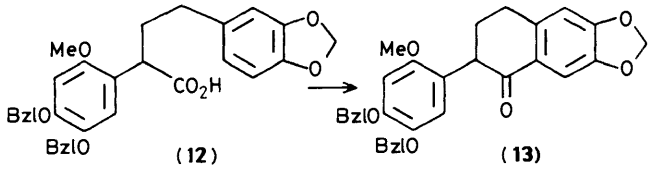
These stimulating results aroused our interest in re-examination of the synthesis of the 2′-isopropoxytetralone (**5b**), although in the synthetic study of fagaronine (**6a**) we prepared the 2′-isopropoxytetralone (**5b**) by treatment with $POCl_3$ in chloroform without potassium carbonate, in spite of formation of the phenolic tetralone (**5a**) as a by-product in 5.8% yield. Treatment of the 2′-isopropoxy acid (**4b**) under the conditions of basic acylation mentioned above gave only the desired

Table 3. Yields (%) of the tetralones (**5**) or (**13**) from the acids (**4**) or (**12**) by treatment with phosphoryl trichloride

Acid (**4**) or (**12**)	Solvent[a]	K_2CO_3[b]	Tetralone (**5**) or (**13**) nonphenolic	Tetralone (**5**) or (**13**) phenolic	Ref.
(**4b**)	$CHCl_3$[c]	+	(**5b**) 71.0	(**5a**) 5.8	lit.[1]
	MeCN[c]		86.9		this paper
(**4d**)	$CHCl_3$[c]	+	(**5d**) 41.6	(**5c**) 19.5[e]	this paper
	MeCN[c]		91.3		this paper
(**4f**)	$CHCl_3$[d]	+	(**5f**) 63.8	(**5e**) 6.8	this paper
	MeCN[c]		78.1		this paper
(**12**)	$CHCl_3$[d]	+	(**13**)		lit.[6]
	MeCN[c]		>61.6		this paper

[a] (**4**) or (**12**)/solvent = 1 g/5—7 ml. [b] 2.2 mol equiv. [c] Contained 5 mol equiv. of $POCl_3$. [d] Contained 10 mol equiv. of $POCl_3$. [e] Showed four spots on t.l.c.

nonphenolic tetralone (**5b**) in 86.9% yield. Then, we also tried to synthesize the tetralone (**13**), bearing benzyloxy groups, from the corresponding methylene acid (**12**) by the basic acylation method, although we already recognised that the acid (**12**) did not provide the nonphenolic product (**13**) on treatment with $POCl_3$ in chloroform in the absence of potassium carbonate. The benzyloxy acid[6] (**12**) yielded no phenolic tetralone under the basic conditions employed but gave the desired nonphenolic one (**13**) in relatively good yield (Table 3, Scheme 3).



Scheme 3.

These experimental results evidently constitute an effective contribution to the synthesis of phenolic benzo[*c*]phenanthridine alkaloids. Moreover, it should be emphasised here that, in general, the acylation of aromatic rings has been performed under various acidic conditions as exemplified by Friedel–Crafts reaction *etc.*, but our results suggested the possibility that the acylation would take place under basic conditions even in the case of intermolecular reaction. Trials are underway in our laboratory to test this hypothesis.

Experimental

All m.p.s were measured on a micro melting-point hot-stage (Yanagimoto) and are uncorrected. I.r. spectra were recorded for Nujol mulls on a Hitachi 215 spectrophotometer. ^{1}H N.m.r. spectra were recorded in $CDCl_3$ solutions on a Hitachi R-24B (60 MHz) spectrometer, unless otherwise stated, with tetramethylsilane as internal reference. All NH and OH signals were confirmed by disappearance of their signals after addition of deuterium oxide. JEOL JNM-4H-100 (100 MHz) and JEOL FX-270 (270 MHz) spectrometers were also used. Mass spectra were measured with a Hitachi RMU-6E spectrometer using a direct-inlet system. For chromatography, silicic acid (100 mesh; Mallinckrodt Chemical Works) and silica gel 60 (70—230 mesh ASTM; Merck) were used, while for t.l.c. and preparative t.l.c. (p.l.c.), silica gel GF_{254} (Merck) was used. Products were identified by i.r., mixed m.p., and t.l.c.

4-*Isopropoxy*-3-*methoxybenzaldehyde* (**8a**).—A suspension of vanillin (30.0 g), isopropyl bromide (28.0 ml), and potassium carbonate (43.6 g) in dimethylformamide (120 ml) was stirred at 50—60 °C for 9.5 h, poured into a large quantity of water, and extracted with diethyl ether. The ethereal solution was washed with 5% aqueous sodium hydroxide, dried (K_2CO_3), and evaporated to dryness under reduced pressure. The oily residue was purified by distillation at 117—120 °C (3 mmHg) [lit.,[7] 150—152 °C (13 mmHg)] to give the *title product* as an oil (34.1 g); $\nu_{max.}$(neat) 1 690 cm^{-1}; δ 1.43 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 3.92 (3 H, s, OMe), 4.69 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 6.95 (1 H, d, *J* 8.5 Hz, 5-H), 7.40 (1 H, d, *J* 2.0 Hz, 2-H), 7.42 (1 H, dd, *J* 8.5 and 2.0 Hz, 6-H), and 9.82 (1 H, s, CHO).

General Method for the Syntheses of the Chalcone Derivatives (**1**).—Equivalent amounts of acetopiperone (**9**) and the benzaldehyde (**8**) were dissolved in a minimum amount of ethanol. The mixture was made alkaline with sodium hydroxide solution and was then stirred at room temperature overnight. After addition of a large amount of water, the precipitate was collected by filtration. Recrystallisation of the crude product from a suitable solvent gave the desired chalcone (**1**).

4-*Isopropoxy*-3-*methoxy*-3′,4′-*methylenedioxychalcone* (**1d**). A mixture of acetopiperone (**9**) (25.4 g) and 4-isopropoxy-3-methoxybenzaldehyde (**8a**) (30.0 g) in ethanol (330 ml) was treated as above with 10% aqueous sodium hydroxide (83 ml), then stirred at room temperature for 14 h to give the *chalcone* (**1d**) as yellow needles (46.2 g), m.p. 121—123 °C (from chloroform–methanol) (Found: C, 70.7; H, 5.9. $C_{20}H_{20}O_5$ requires C, 70.6; H, 5.9%); $\nu_{max.}$ 1 660 cm^{-1}; δ (100 MHz) 1.39 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 3.91 (3 H, s, OMe), 4.60 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 6.05 (2 H, s, OCH$_2$O), 6.88 (2 H, d, *J* 8.0 Hz, 5- and 5′-H), 7.15 (1 H, s, 2-H), 7.19 (1 H, d, *J* 8.0 Hz, 6-H), 7.31 (1 H, d, *J* 15.0 Hz, CH=C*H*CO), 7.51 (1 H, d, *J* 2.0 Hz, 2′-H), 7.63 (1 H, dd, *J* 8.0 and 2.0 Hz, 6′-H), and 7.74 (1 H, d, *J* 15.0 Hz, ArC*H*=CH).

3-*Isopropoxy*-4-*methoxy*-3′,4′-*methylenedioxychlacone* (**1f**). A mixture of acetopiperone (**9**) (26.2 g) and 3-isopropoxy-4-methoxybenzaldehyde[1] (**8b**) (31.2 g) in ethanol (402 ml) was treated as above with 10% aqueous sodium hydroxide (110 ml), then stirred at room temperature overnight to give the *chalone* (**1f**) as yellow prisms (49.4 g), m.p. 136—137 °C (Found: C, 70.7; H, 5.9%); $\nu_{max.}$ 1 650 cm^{-1}; δ 1.39 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 3.88 (3 H, s, OMe), 4.58 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 6.03 (2 H, s, OCH$_2$O), 6.86 (2 H, d, *J* 8.0 Hz, 5- and 5′-H), 7.20 (1 H, d, *J* 2.0 Hz, 2-H), 7.22 (1 H, dd, *J* 8.0 and 2.0 Hz, 6-H), 7.26 (1 H, d, *J* 15.5 Hz, CH=C*H*CO), 7.50 (1 H, d, *J* 2.0 Hz, 2′-H), 7.62 (1 H, dd, *J* 8.0 and 2.0 Hz, 6′-H), and 7.75 (1 H, d, *J* 15.5 Hz, ArC*H*=CH).

General Method for the Hydrocyanation of the Chalcones (**1**) *to give* 2,4-*Diaryl*-4-*oxobutyronitriles* (**2**).—The starting chalcone (**1**) was dissolved in a minimum amount of hot ethyl cellosolve containing acetic acid. An aqueous solution of potassium cyanide was added to the mixture at about 120 °C. The mixture was heated at the same temperature with monitoring by t.l.c., and finally poured into a large amount of water. The precipitate was collected by filtration and recrystallised from a suitable solvent to give the desired nitrile (**2**).

2-(4-*Isopropoxy*-3-*methoxyphenyl*)-4-(3′,4′-*methylenedioxyphenyl*)-4-*oxobutyronitrile* (**2d**). A solution of the 4-isopropoxychalcone (**1d**) (63.2 g) in ethyl cellosolve (290 ml) containing acetic acid (13 ml) was treated as above with a solution of potassium cyanide (28.5 g) in water (53 ml); the mixture was then heated for 8 min to give a crude product. Column chromatography with benzene gave the *nitrile* (**2d**) as prisms (59.0 g), m.p. 115—116 °C (from chloroform–methanol) (Found: C, 68.6; H, 5.7; N, 3.8. $C_{21}H_{21}NO_5$ requires C, 68.65; H, 5.8; N, 3.8%); $\nu_{max.}$ 2 240 and 1 675 cm^{-1}; δ 1.35 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 3.32 (1 H, dd, *J* 18.0 and 7.0 Hz, CHC*H*$_A$H$_B$CO), 3.68 (1 H, dd, *J* 18.0 and 7.0 Hz, CHCH$_A$*H*$_B$CO), 3.86 (3 H, s, OMe), 4.20—4.80 (2 H, m, ArC*H*CH$_2$ and OC*H*Me$_2$), 6.03 (2 H, s, OCH$_2$O), 6.81 (1 H, d, *J* 8.0 Hz, 5′-H), 6.89 (3 H, s, ArH), 7.39 (1 H, d, *J* 2.0 Hz, 2′-H), and 7.50 (1 H, dd, *J* 8.0 and 2.0 Hz, 6′-H).

2-(3-*Isopropoxy*-4-*methoxyphenyl*)-4-(3′,4′-*methylenedioxyphenyl*)-4-*oxobutyronitrile* (**2f**). A solution of the 3-isopropoxychalcone (**1f**) (50.0 g) in ethyl cellosolve (230 ml) containing acetic acid (10 ml) was treated as above with a solution of potassium cyanide (22.0 g) in water (42 ml); the mixture was then heated for 8 min to give the *nitrile* (**2f**) as prisms (47.5 g), m.p. 121.5—123 °C (from chloroform–methanol) (Found: C, 68.6; H, 5.8; N, 3.8%); $\nu_{max.}$ 2 245 and 1 670 cm^{-1}; δ 1.35 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 3.31 (1 H, dd, *J* 18.0 and 7.0 Hz, CHC*H*$_A$CH$_B$CO), 3.65 (1 H, dd, *J* 18.0 and 7.0 Hz, CHCH$_A$*H*$_B$CO), 3.83 (3 H, s, OMe), 4.47 (1 H, t, *J* 7.0 Hz, ArC*H*CH$_2$), 4.53 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 6.03 (2 H, s, OCH$_2$O), 6.81 (1 H, d, *J* 8.5 Hz, 5′-H), 6.72—7.07 (3 H, m, ArH), 7.37 (1 H, d, *J* 2.0 Hz, 2′-H), and 7.48 (1 H, dd, *J* 8.5 and 2.0 Hz, 6′-H).

General Method for the Hydrolysis of the Butyronitriles (**2**) *to the* 2,4-*Diaryl*-4-*oxobutyric Acids* (**3**).—The butyronitrile (**2**) was suspended in a solution of sodium hydroxide in aqueous ethanol and the suspension was refluxed under argon until a blue-black precipitate could not be formed by addition of *ca.* 10% hydrochloric acid to a portion of the reaction solution. The reaction mixture was poured onto water and extracted with diethyl ether. The aqueous solution was acidified with 10% hydrochloric acid and the precipitate was collected by filtration. Recrystallisation of the crude material from an appropriate solvent gave the desired keto acid (**3**).

2-(4-*Isopropoxy*-3-*methoxyphenyl*)-4-(3′,4′-*methylenedioxyphenyl*)-4-*oxobutyric Acid* (**3d**). A solution of the butyronitrile (**2d**) (57.4 g) in water (660 ml) containing ethanol (280 ml) and sodium hydroxide (61.6 g) was treated as above, then refluxed for 5 h, to give the *acid* (**3d**) as prisms (52.5 g), m.p. 159—161 °C (from methanol) (Found: C, 64.9; H, 5.7. $C_{21}H_{22}O_7$ requires C, 65.3; H, 5.7%); $\nu_{max.}$ 3 600—2 850br, 1 725, and 1 675 cm^{-1}; δ 1.35 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 3.16 (1 H, dd, *J* 18.0 and 4.0 Hz, CHC*H*$_A$H$_B$CO), 3.79 (1 H, dd, *J* 18.0 and 10.0 Hz, CHCH$_A$*H*$_B$CO), 3.83 (3 H, s, OMe), 4.22 (1 H, dd, *J* 10.0 and 4.0 Hz, ArC*H*CH$_2$), 4.48 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 6.01 (2 H, s, OCH$_2$O), 6.14 (1 H, br s, CO$_2$H), 6.79 (1 H, d, *J* 8.0 Hz, 5′-H), 6.83 (3 H, s, ArH), 7.39 (1 H, d, *J* 2.0 Hz, 2′-H), and 7.55 (1 H, dd, *J* 8.0 and 2.0 Hz, 6′-H).

2-(3-*Isopropoxy*-4-*methoxyphenyl*)-4-(3′,4′-*methylenedioxyphenyl*)-4-*oxobutyric Acid* (**3f**). A solution of the butyronitrile (**2f**) (25.0 g) in water (290 ml) containing sodium hydroxide (26.9 g) and ethanol (121 ml) was treated as above, then refluxed for 5 h, to give the *acid* (**3f**) as prisms (22.3 g), m.p. 167—168.5 °C (from benzene–hexane followed by methanol) (Found: C, 65.4; H, 5.7%); $\nu_{max.}$ 1 705 and 1 680 cm^{-1}; δ 1.33 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 3.15 (1 H, dd, *J* 17.0 and 4.0 Hz, CHC*H*$_A$H$_B$CO), 3.77 (1 H, dd, *J* 17.0 and 9.5 Hz, CHCH$_A$*H*$_B$CO), 3.81 (3 H, s, OMe), 4.20 (1 H, dd, *J* 9.5 and 4.0 Hz, ArC*H*CH$_2$), 4.51 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 4.98 (1 H, br s, CO$_2$H), 6.01 (2 H, s, OCH$_2$O), 6.80 (1 H, d, *J* 8.0 Hz, 5′-H), 6.87 (3 H, s, ArH), 7.39 (1 H, d, *J* 1.5 Hz, 2′-H), and 7.55 (1 H, dd, *J* 8.0 and 1.5 Hz, 6′-H).

General Method for the Hydrogenolysis of the Keto Acids (**3**) *to the* 2,4-*Diarylbutyric Acids* (**4**).—An aqueous solution of palladium(II) chloride* and a corresponding amount of Norit for preparation of 10% palladium–charcoal were added to a solution of the keto acid (**3**) in acetic acid. The mixture was hydrogenated at room temperature under atmospheric pressure until absorption of hydrogen ceased. After removal of the catalyst by filtration, the filtrate was evaporated to dryness under reduced pressure and the residue was dissolved in chloroform. The solution was washed with water, dried ($MgSO_4$), and then evaporated to dryness under reduced pressure. Recrystallisation of the residue from an appropriate solvent afforded the desired butyric acid (**4**).

2-(4-*Isopropoxy*-3-*methoxyphenyl*)-4-(3,4-*methylenedioxyphenyl*)*butyric Acid* (**4d**). A solution of the keto acid (**3d**) (12.0 g) in acetic acid (230 ml) was treated as above with the palladium chloride solution (48 ml) and Norit (4.30 g) to give the *acid* (**4d**) as prisms (10.2 g), m.p. 124—125 °C (from diethyl ether–hexane) (Found: C, 67.9; H, 6.5. $C_{21}H_{24}O_6$ requires C, 67.7; H, 6.5%); $\nu_{max.}$ 1 685 cm^{-1}; δ 1.35 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 1.92—2.70 (4 H, m, 3- and 4-H$_2$), 3.26—3.63 (1 H, m, 2-H), 3.83 (3 H, s, OMe), 4.48 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 5.88 (2 H, s, OCH$_2$O), 6.61 (3 H, br s, ArH), 6.81 (3 H, s, ArH), and 8.64 (1 H, br s, CO$_2$H).

2-(3-*Isopropoxy*-4-*methoxyphenyl*)-4-(3,4-*methylenedioxyphenyl*)*butyric Acid* (**4f**). A solution of the keto acid (**3f**) (25.1 g) in acetic acid (1.2 l) was treated as above with the palladium chloride solution (100 ml) and Norit (9.00 g) to give the *acid* (**4f**) as an oil (23.6 g). Purification of a part of this material by p.l.c. with chloroform–methanol (15:1) gave needles, m.p. 71—75 °C (from diethyl ether–hexane) (Found: C, 67.85; H, 6.5%); $\nu_{max.}$ 1 705 cm^{-1}; δ 1.33 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 2.00—2.75 (4 H, m, 3- and 4-H$_2$), 3.30—3.65 (1 H, m, 2-H), 3.81 (3 H, s, OMe), 4.49 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 5.98 (2 H, s, OCH$_2$O), 6.42—7.00 (1 H, br s, CO$_2$H), 6.60 (3 H, diffused s, ArH), and 6.82 (3 H, s, ArH).

The crude material was used in the subsequent step without purification.

Treatment of the Acid (**4d**) *with Phosphoryl Trichloride in Chloroform to give* 2-(4′-*Isopropoxy*-3′-*methoxyphenyl*)-6,7-*methylenedioxy*-3,4-*dihydronaphthalen*-1(2H)-*one* (**5d**).—A mixture of the acid (**4d**) (0.20 g) and phosphoryl trichloride (0.27 ml) in chloroform (1 ml) was heated at 78—80 °C for 160 min. The mixture was poured onto ice–water, made alkaline with 5% aqueous sodium hydroxide, and extracted with diethyl ether. The ethereal solution was dried (K_2CO_3) and evaporated to dryness. Column chromatography of the residue was achieved with benzene–ethyl acetate (10:1) to give the *tetralone* (**5d**) as prisms (0.079 g), m.p. 128—131 °C, which was

* Anhydrous palladium(II) chloride (1.0 g) was dissolved in a mixture of conc. hydrochloric acid (2.5 ml) and water (6.0 ml). The total volume of the resulting solution was then made up to 60 ml by addition of water.

recrystallised from methanol (Found: C, 71.3; H, 6.3. $C_{21}H_{22}O_5$ requires C, 71.2; H, 6.3%); $\nu_{max.}$ 1 670 cm^{-1}; δ 1.34 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 2.07—2.59 (2 H, m, 3-H_2), 2.97 (2 H, t, *J* 6.0 Hz, 4-H_2), 3.67 (1 H, t, *J* 8.0 Hz, 2-H), 3.81 (3 H, s, OMe), 4.47 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 5.98 (2 H, s, OCH_2O), 6.63 (1 H, d, *J* 9.0 Hz, 5′- or 6′-H), 6.65 (1 H, s, 5-H), 6.70 (1 H, s, 2′-H), 6.86 (1 H, d, *J* 9.0 Hz, 6′- or 5′-H), and 7.50 (1 H, s, 8-H).

The alkaline mother liquor was acidified with 10% hydrochloric acid and extracted with chloroform. The chloroform solution was dried ($MgSO_4$), and evaporated to dryness under reduced pressure. The residue (0.033 g) showed four spots on t.l.c. with benzene–ethyl acetate (10:1).

Treatment of the Acid (**4f**) *with Phosphoryl Trichloride in Chloroform.*—A mixture of the acid (**4f**) (7.60 g) and phosphoryl trichloride (20.7 ml) in chloroform (36.5 ml) was heated at 78—80 °C for 3 h. The mixture was poured onto ice–water, and extracted with diethyl ether. The ethereal solution was washed with 5% aqueous sodium hydroxide, dried (K_2CO_3), and evaporated to dryness.

(*a*) 2-(3′-*Isopropoxy*-4′-*methoxyphenyl*)-6,7-*methylenedioxy*-3,4-*dihydronaphthalen*-1(2H)-*one* (**5f**). Recrystallisation of the residue from chloroform–methanol gave the *tetralone* (**5f**) as needles (4.61 g), m.p. 108—110 °C (Found: C, 71.1; H, 6.3%); $\nu_{max.}$ 1 670 cm^{-1}; δ 1.33 (6 H, d, *J* 6.0 Hz, CH*Me*$_2$), 2.20—2.56 (2 H, m, 3-H_2), 2.96 (2 H, t, *J* 6.0 Hz, 4-H_2), 3.67 (1 H, t, *J* 8.0 Hz, 2-H), 3.81 (3 H, s, OMe), 4.47 (1 H, septet, *J* 6.0 Hz, OC*H*Me$_2$), 5.99 (2 H, s, OCH_2O), 6.65 (1 H, s, 5-H), 6.67 (1 H, d, *J* 8.5 Hz, 5′- or 6′-H), 6.72 (1 H, s, 2′-H), 6.85 (1 H, d, *J* 8.5 Hz, 6′- or 5′-H), and 7.50 (1 H, s, 8-H).

(*b*) 2-(3′-*Hydroxy*-4′-*methoxyphenyl*)-6,7-*methylenedioxy*-3,4-*dihydronaphthalen*-1(2H)-*one* (**5e**). The aqueous sodium hydroxide washings were acidified with 10% hydrochloric acid and extracted with diethyl ether. The ethereal solution was washed with 5% aqueous sodium hydrogen carbonate, then dried ($MgSO_4$), and evaporated to dryness under reduced pressure. Recrystallisation of the residue from chloroform–methanol gave the *tetralone* (**5e**) as prisms (0.433 g), m.p. 183—186 °C (Found: C, 68.9; H, 5.2. $C_{18}H_{16}O_5$ requires C, 69.2; H, 5.2%); $\nu_{max.}$ 3 330 and 1 665 cm^{-1}; δ 2.19—2.54 (2 H, m, 3-H_2), 2.93 (2 H, t, *J* 6.0 Hz, 4-H_2), 3.64 (1 H, t, *J* 7.5 Hz, 2-H), 3.86 (3 H, s, OMe), 5.65 (1 H, br s, OH), 5.98 (2 H, s, OCH_2O), 6.60 (1 H, dd, *J* 8.0 and 2.0 Hz, 6′-H), 6.66 (1 H, s, 5-H), 6.75 (1 H, br s, 2′-H), 6.81 (1 H, d, *J* 8.0 Hz, 5′-H), and 7.49 (1 H, s, 8-H).

Treatment of the Acid (**4d**) *with Phosphoryl Trichloride under Various Basic Conditions.*—(i) *With potassium carbonate in chloroform.* After a suspension of the acid (**4d**) (5.00 g, 13.4 mmol) in chloroform (25 ml) containing potassium carbonate (20.0 g, 145 mmol) had been stirred at room temperature for some time, phosphoryl trichloride [(4.4 ml, 47.2 mmol), (5.7 ml, 61.1 mmol), (6.7 ml, 71.9 mmol), (8.1 ml, 86.9 mmol), (9.4 ml, 101 mmol)] was added to the mixture which was then heated at 80 °C for 70 min. The reaction mixture was poured onto ice–water, made alkaline with 5% aqueous sodium hydroxide, and extracted with diethyl ether. The ethereal solution was dried (K_2CO_3), and evaporated to dryness under reduced pressure. Recrystallisation of the residue from benzene–hexane gave the desired tetralone (**5d**) as prisms, m.p. 130—131 °C (see the yields in Table 1).

(ii) *With potassium carbonate in benzene.* A suspension of the acid (**4d**) (0.16 g), phosphoryl trichloride (0.30 ml), and potassium carbonate (0.64 g) in benzene (0.8 ml) was treated as above, under reflux for 6 h, to give the desired tetralone (**5d**) (0.064 g).

(iii) *With potassium carbonate in nitrobenzene.* A suspension of the acid (**4d**) (0.20 g), potassium carbonate (0.081 g), and phosphoryl trichloride (0.5 ml) in nitrobenzene (1.0 ml) was heated at 60 °C for 50 min, poured onto a large amount of water, and made alkaline with 5% aqueous sodium hydroxide. After removal of nitrobenzene by steam distillation, the reaction mixture was treated as above to give the desired tetralone (**5d**) (0.098 g).

(iv) *With potassium carbonate in carbon tetrachloride.* A suspension of the acid (**4d**) (0.801 g), potassium carbonate (0.650 g), and phosphoryl trichloride (1.0 ml) in carbon tetrachloride (4.0 ml) was heated at 60 °C for 7 h to give the desired tetralone (**5d**) (0.548 g).

(v) *With potassium carbonate in dimethyl sulphoxide.* A suspension of the acid (**4d**) (0.16 g), potassium carbonate (0.13 g), and phosphoryl trichloride (0.2 ml) in DMSO (0.8 ml) was heated at 60 °C for 90 min to give a crude product (0.070 g) which did not show a spot due to the desired tetralone (**5d**) on t.l.c.

(vi) *With potassium carbonate without solvent.* The acid (**4d**) (0.50 g) was added to a suspension of potassium carbonate (0.19 g) in phosphoryl trichloride (1.25 ml) at room temperature. The reaction mixture was refluxed for 1.5 h, then treated as above to give the desired tetralone (**5d**) (0.31 g).

(vii) *With triethylamine in acetonitrile.* Phosphoryl trichloride (0.20 ml) was added dropwise to a solution of the acid (**4d**) (0.16 g) in acetonitrile (0.70 ml) containing triethylamine (0.13 ml) at room temperature. The mixture was heated at 60 °C for 75 min. Treatment of the reaction mixture as above then gave a crude product (0.034 g) showing many spots on t.l.c.

General Method for the Intramolecular Cyclisation of the Acids (**4**) *with Phosphoryl Trichloride in Acetonitrile in the Presence of Potassium Carbonate.*—Phosphoryl trichloride (5.0 mol equiv.) was added portionwise to an ice-cooled solution of the acid (**4**) (1.0 mol equiv.) in an appropriate amount of acetonitrile containing potassium carbonate (2.2 mol equiv.). The reaction mixture was heated at 55—60 °C with monitoring by t.l.c. When the reaction was over, the reaction mixture was poured onto ice–water and extracted with diethyl ether or chloroform. The organic layer was washed with 5% aqueous sodium hydroxide, dried (K_2CO_3), and evaporated to dryness. Recrystallisation of the residue from a suitable solvent gave the desired tetralone (**5**).

2-(4-*Isopropoxy*-3-*methoxyphenyl*)-6,7-*methylenedioxy*-3,4-*dihydronaphthalen*-1(2H)-*one* (**5d**). A suspension of the acid (**4d**) (5.00 g), phosphoryl trichloride (6.30 ml), and potassium carbonate (4.08 g) in acetonitrile (34.0 ml) was heated at 55—60 °C for 3 h to give the desired 4-isopropoxytetralone (**5d**) (4.34 g).

2-(3-*Isopropoxy*-4-*methoxyphenyl*)-6,7-*methylenedioxy*-3,4-*dihydronaphthalen*-1(2H)-*one* (**5f**). A suspension of the acid (**4f**) (0.801 g), phosphoryl trichloride (1.0 ml), and potassium carbonate (0.654 g) in acetonitrile (4.0 ml) was heated at 55—60 °C for 90 min to give a crude product. Column chromatography with benzene–ethyl acetate (20:1 ⟶ 10:1) gave prisms (0.595 g), m.p. 110—112 °C (from chloroform–methanol). This material was identical with the desired tetralone (**5f**) obtained by treatment with phosphoryl trichloride in the absence of potassium carbonate in chloroform.

2-(3,4-*Dimethoxyphenyl*)-6-*isopropoxy*-7-*methoxy*-3,4-*dihydronaphthalen*-1(2H)-*one* (**5b**). A suspension of the acid[1] (**4b**) (4.00 g), phosphoryl trichloride (4.80 ml), and potassium carbonate (3.13 g) in acetonitrile (20.0 ml) was heated at 55—60 °C for 2 h to give prisms (3.32 g), m.p. 121—123 °C. This material was identical with a sample of 2-(3,4-dimethoxyphenyl)-6-isopropoxy-7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**5b**) prepared in the course of synthetic work of fagaronine (**6a**) by treatment of the acid (**4b**) with phosphoryl trichloride in the absence of potassium carbonate in chloroform.

2-(4,5-*Dibenzyloxy*-2-*methoxyphenyl*)-6,7-*methylenedioxy*-3,4-*dihydronaphthalen*-1(2H)-*one* (**13**). A suspension of the acid[6] (**12**) (1.13 g) and phosphoryl trichloride (1.0 ml) in acetonitrile (7.8 ml) containing potassium carbonate (0.652 g) was heated at 55—60 °C for 90 min and extracted with chloroform. The crude material was purified by column chromatography with benzene–ethyl acetate (40:1) to give prisms (0.666 g), m.p. 142—143.5 °C (from benzene–hexane) (lit.,[6] 139—141 °C). This material was identical with a sample of 2-(4,5-dibenzyloxy-2-methoxyphenyl)-6,7-methylenedioxy-3,4-dihydronaphthalen-1(2*H*)-one (**13**) prepared by treatment with thionyl chloride and tin(IV) chloride.

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