Total Synthesis of (±)-Picropodophyllone

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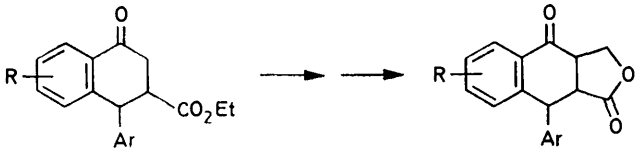
Following model studies, the synthesis of (±)-picropodophyllone was completed by first cyclopropanating the appropriate chalcone (11) with ethoxycarbonyl dimethylsulphonium methylide. Treatment of the resulting cyclopropyl ketone with stannic chloride in either benzene or methylene chloride failed but in nitromethane the tetralone (10a) was formed. The lactone ring was completed using formaldehyde with an overall yield based on chalcone of 40%.

We have found [1] that 1-aryltetralones are readily synthesised by acid-catalysed rearrangement of aryl-substituted cyclopropyl aryl ketones. These later ketones are readily available by the cyclopropanation [1] of chalcones.[2] Subsequently we noted that substituted tetralones (1) could potentially be prepared by a similar route. This is important since the transformation of (1) to (2) is now such a well established procedure [3] that tetralones of type (1) are common synthetic precursors of lignan lactones.[3,4] We now report the results of our investigation of this route to tetralones (1) [5] and the extension of this methodology to the synthesis of (±)-picropodophyllone.[4]



(1) (2)

Our initial objectives were to (*a*) synthesise the appropriate cyclopropyl ketone and (*b*) investigate the acid-catalysed rearrangement of this ketone. The model system (Scheme 1) was chosen for investigation.

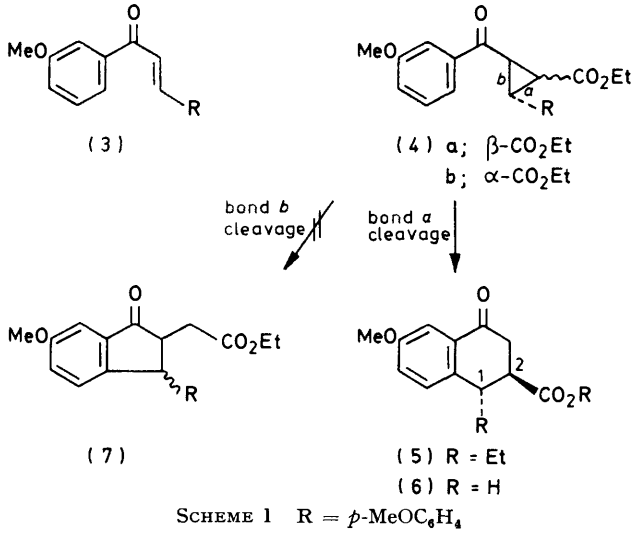
Ethoxycarbonylsulphonium methylides (8a—b) are well established cyclopropanating agents [6] of enones. Their use suggested an attractive route to cyclopropyl ketoesters (4). However, this cyclopropanation had been accomplished with one chalcone only, and in very low yield, using the ylide (8a). An efficient cyclopropanation of chalcone had been reported by Trost and his coworkers [8] using the more reactive carboxylate ylide from (8c). However this route would give cyclopropyl ketoacids and would require esterification, an additional step, to give the desired cyclopropyl ketoesters (4).

The cyclopropanation of compound (3) was attempted using the ethoxycarbonyl ylide (8b).[9] When compound (3) was heated under reflux with the ylide (8b) in tetrahydrofuran for 23 h, the cyclopropyl ketoester (4) was obtained in 94% isolated yield. The oily product was a separable 1 : 1 mixture of (4a) and (4b) contaminated by small amounts of other isomers. The stereochemistry of (4a) and (4b) was assigned by comparison (n.m.r.) with known, closely related aryl cyclopropyl ketoesters.[8] Subsequently, it was found that the reaction was complete when stirred for 4 h at room temperature. No side-products were detectable.

$R_2S = CHCO_2R^1$

(8)

a; R = Ph; R^1 = Et
b; R = Me; R^1 = Et
c; R = Me; R^1 = H



(3) (4) a; β-CO_2Et
b; α-CO_2Et
(7) (5) R = Et
(6) R = H

Scheme 1 R = *p*-$MeOC_6H_4$

The cyclopropyl ketoester (4a) was then treated with stannic chloride in benzene for 9 h at room temperature. The crystalline tetralone (5) was obtained in 80% yield. Bond *b* cleavage (Scheme 1) with formation of the indanone (7) was never observed.

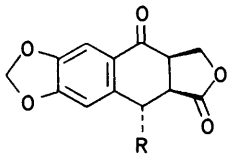
The appearance of 1-H at δ 4.59 ($J_{1,2}$ 7.5 Hz) served to establish the *trans*-relationship between 1-H and 2-H of the tetralone (5) by analogy with closely related systems.[10,11] This *trans*-assignment was further supported by the fact that no epimerisation was observed when the tetralone (5) or its ketoacid (6) was heated under reflux in aqueous methanolic sodium hydroxide for 3 h.

The reaction was invariably stereospecific. None of the diastereoisomer of (5) was isolated. The epimer (4b) or a mixture of (4a) and (4b) upon treatment with stannic chloride in either benzene or stannic chloride gave the same product.

Following the successful completion of this model

study (Scheme 1) the same methodology was applied to the synthesis of (±)-picropodophyllone (9).

Picropodophyllone and related lignan lactones have received considerable attention as cancer chemotherapeutic agents.[12] Accordingly much effort has been expended on new and improved syntheses of these lignans.[10,13,14] Podophyllotoxin itself has been synthesised *via* the tetralone (10).[15]



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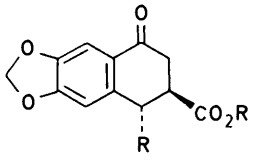
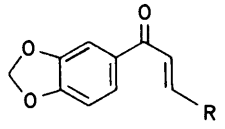


(10) a; R = Et
b; R = H



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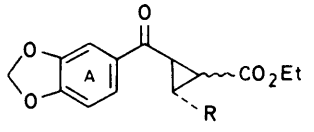


(12) a; β-CO_2Et
b; α-CO_2Et

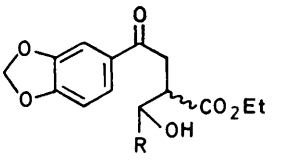
R = 3,4,5-$(MeO)_3C_6H_2$

The initial objective was the tetralone (10). Accordingly the chalcone (11) [2] was cyclopropanated as above to give the desired product (12) as a 1 : 1 mixture of epimers in 95% yield.

However, attempted cyclisation of (12a) or (12b) separately or as a mixture with stannic chloride under a variety of reaction conditions, failed.[16] None of compound (10) was formed. Varying yields of compounds (13) and (14) as diastereomeric mixtures, were obtained following basic work-up. The structure of (14) was tentatively assigned on the basis that it changed to (13) with time.

The reluctance of compound (12) to form the tetralone (10) prompted consideration of related studies. Both (15) [14,17] and (16) [13] cyclise to the corresponding tetralins *via* their corresponding benzyl carbocations. The alkene (17) [17] however, is apparently stable towards acid. From these results we conclude that the failure of (12) to cyclise and yet undergo cyclopropyl ring cleavage is consistent with a combination of two effects (*a*) the three vicinal methoxy-groups are sterically prohibited from stabilising the benzyl carbocation and have a net deactivating effect, as discussed by Gensler [18] and (*b*) ring A in (12) is deactivated by the neighbouring carbonyl group.

These results can be accommodated by the mechanistic pathways outlined in Scheme 2. Attack of the carbonyl group on the initially formed carbocation intermediate (18) is, we suggest, stabilised by the formation of the oxonium ion (19). We consider that this (route b) is much faster than aryl ring attack (route a), with the



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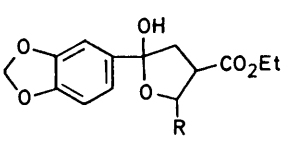

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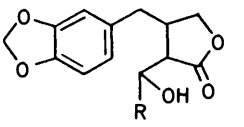

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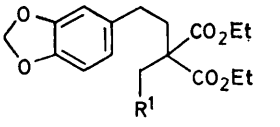

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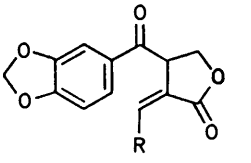
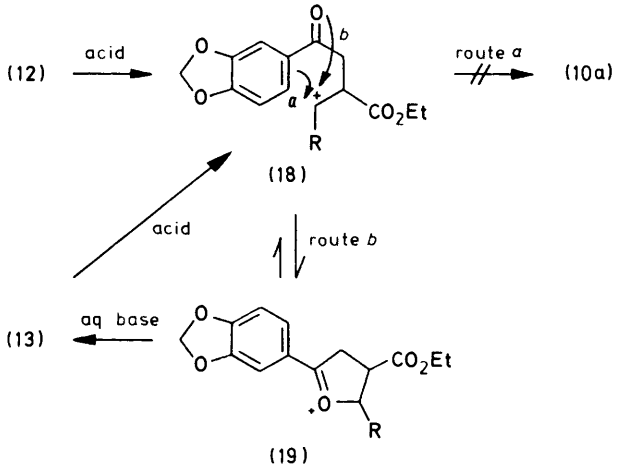


(17)

R = 3,4,5-$(MeO)_3C_6H_2$; R^1 = 3,5-$(MeO)_2$-4-HO-C_6H_2

equilibrium essentially on the side of (19) due to the instability of the 3,4,5-trimethoxybenzyl carbocation system.

Although we have as yet no direct evidence for the formation of the oxonium ion (19) such intermediates have been detected in related systems and are known



SCHEME 2 R = 3,4,5-$(MeO)_3C_6H_2$

to yield γ-hydroxy-ketones after quenching with aqueous base.[19] In addition, involvement of compound (19) explains both the formation of (13) and the reason why (10a) is not formed.

Consistent with this mechanism is our finding that the carbinols (13) did not cyclise to (10a) under the usual conditions and were recovered.

Eventually, the tetralone (10a) was found to be the

main product when the ketoester (12) was treated with stannic chloride in nitromethane. The dramatic effect of this solvent in Lewis acid-catalysed reactions have been observed by others.[16b,20] Successful cyclisation was most likely the result of a solvent-induced shift in the equilibrium between (18) and (19) (Scheme 2).

The results obtained upon treatment of compound (12) with Lewis acids in nitromethane under a variety of reaction conditions are shown in (Table 1). The *trans*-

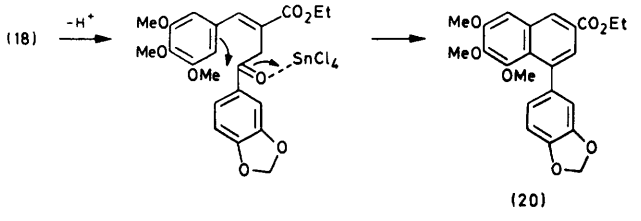
TABLE 1

Cyclisation of compound (12) in nitromethane

Reactant (mg)	Acid (ml)	$MeNO_2$ (ml)	Conditions [a]	Product [(yield, %)] [b]
(12a) (140)	$SnCl_4$, (0.04)	8	R.t. (6 d)	(10a) [43], (13) [31] [c], (20) [trace]
(12b) (210)	$SnCl_4$, (0.08)	16	R.t. (4 d)	(10a) [53], (13) [40] [c], (20) [trace]
(12b) (220)	,,	,,	R.t. (16 d)	(10a) [50], (13) [31] [c], 20) [7]
(12) (220)	$BF_3{\cdot}Et_2O$	10	R.t. (15 d)	(10a) [57], (13) [10] [c], (20) [9]
(12) (50)	$SnCl_4$	5	80—100 °C (1 h)	tars

[a] All reactions were carried out under nitrogen. Aqueous NaOH (5%) work-up. R.t. = room temperature. [b] Isolated yields (preparative t.l.c.). [c] Two diastereoisomers (n.m.r.).

tetralone only was formed. The use of the epimers (12a) and (12b) either separately or as a mixture and the use of longer reaction times had no apparent effect on the yields under these conditions. The alcohol (13) was always produced as the main side product. Higher temperature gave only intractable tars. Boron trifluoride–diethyl ether was somewhat more effective and produced compound (10a) in 57% isolated yield. Close



SCHEME 3

examination (t.l.c.) of compounds (12a) and (12b) in stannic chloride–nitromethane solution at 0 °C showed that (12a) epimerised to (12b) within 10 min; (12b) did not rearrange to (12a). This is consistent with a very recent report.[21]

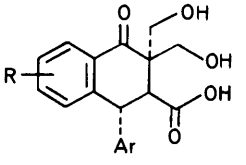
The structure of the arylnaphthalene (20), was deduced from its spectral data.[22] The provisional mechanism (Scheme 3) of formation of (20) is consistent with the observation that no 1-arylnaphthalenes are formed in the absence of the ethoxycarbonyl group.[1] Similar products have been noted by Newman [23] when he reacted related ketones with phosphorus pentachloride. The remaining carbon required for lactone ring formation has been introduced both *via* ethyl formate [18,24] and *via* formaldehyde.[10,13,25-27] Though variable results had been experienced using the latter method, we adopted this approach.

It was decided to concentrate on optimising the yield of the bis-hydroxymethyl derivative (21) since (*a*) it had been found difficult to control mono-hydroxymethyl derivative formation; (*b*) in contrast to the mono-hydroxymethyl derivative of the dibenzocycloctadiene analogue,[26] in the tetralone series it resisted lactonisation,[25,27] probably for steric reasons; (*c*) the mono-hydroxymethyl derivative readily dehydrated;[27] and (*d*) with excess of formaldehyde the bis-hydroxymethyl derivative is formed exclusively.[25,27]

Our results on aldol hydroxymethylation of model tetralones and (10b) under a variety of conditions are shown in Table 2. Hitherto unobserved Cannizzaro reduction products, *i.e.* (23) and (24) were encountered. This side reaction had been observed previously only in the dibenzocyclo-octadiene system.[26]

Finally the hydroxymethyl group in (26) was removed as previously described [13] using an excess of Jones reagent in acetone to produce picropodophyllone (9) in 72% yield after preparative thin layer chromatography.

Our synthetic (±)-picropodophyllone (9) gave n.m.r., i.r., and t.l.c. data in different solvent systems identical with data obtained on authentic (—)-picropodophyllone.



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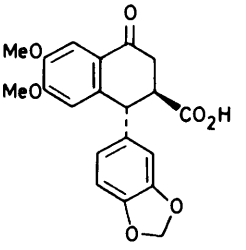

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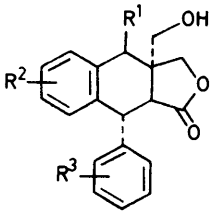

(23) R^1 = HO~ ; R^2 = 3-MeO; R^3 = 4-MeO
(24) R^1 = HO~ ; R^2 = 3,4-$(MeO)_2$; R^3 = 3,4-(CH_2O_2)
(25) R^1 = O= ; R^2 = 3,4-$(MeO)_2$; R^3 = 3,4-(CH_2O_2)
(26) R^1 = O= ; R^2 = 3,4-(CH_2O_2); R^3 = 3,4,5-$(MeO)_3$

TABLE 2

Aldol hydroxymethylation

Tetralone (mg)	Aq. base (5%, ml)	Added solvent (ml)	Formaldehyde [c]	Time (h)	Product [yield, %] [a]
(6) [110]	NaOH (5)	H_2O (5)	p-F (250)	23	(23) [75]
(6) [140]	KOH (5)	—	40% F (2.5)	24	(23) [50]
(22) [b] [200]	NaOH (8)	H_2O (6)	p-F (500)	23	(25) [41]
(22) [150]	NaOH (8)	H_2O (10)	p-F (500)	38	(24) [52]
(22) [180]	NaOH (5)		p-F (600)	96	(24) [50]
(22) [200]	KOH (5)		40% F (8)	48	(25) [85]
(10b) [270]	NaOH (3)		40% F (1.2)	24	(26) [33]
(10b) [125]	NaOH (3)		40% F (3)	30	(26) [80

[a] Isolated yield. [b] Synthesis to be reported elsewhere. [c] p-F = *p*-Formaldehyde (mg) and 40% F = 40% formalin (ml).

Since (9) has been converted [15,18] into podophyllotoxin, this route to (9) constitutes a new total synthesis of podophyllotoxin. The overall yield of picropodophyllone (9) from the chalcone (11) by the novel four-step sequence was 40%.

The successful synthesis of (9), a companion of antitumour podophyllotoxin illustrates the synthetic potential of the acid-catalysed cyclisation of arylcyclopropanes. We anticipate that this new methodology will find extensive use in the synthesis of natural lignans as a result of its generality and efficiency.

EXPERIMENTAL

General procedures were as detailed previously.[1]

General Procedure. Synthesis of Cyclopropyl Ketoesters from Chalcones with Ethoxycarbonyldimethylsulphonium Methylide (8b).—To a stirred suspension of ethoxycarbonylmethyl dimethylsulphonium bromide [9] (3 mmol) in tetrahydrofuran (THF, freshly distilled from lithium aluminium hydride; 6 ml), was added in one portion a dispersion of sodium hydride in mineral oil (3.2 mmol) at room temperature under nitrogen. The mixture was then stirred at room temperature for 2—3 h. To the ylide solution, a solution of the chalcone (2 mmol) in THF (10 ml) was added (*via* a syringe). After being stirred at room temperature for *ca.* 20 min, the reaction mixture was heated under reflux for 23—24 h. The cooled solution was diluted with water, acidified (10% HCl), and extracted with chloroform. The extracts were washed with water, dried (brine, sodium sulphate), and concentrated. The light petroleum-insoluble residual oil was purified by p.l.c. (diethyl ether–light petroleum) to yield the pure product.

Ethyl 2-(4-Methoxyphenyl)-3-(3-methoxyphenylcarbonyl)-cyclopropanecarboxylate (4).—Heating of the chalcone (3) [2] (600 mg, 2.4 mmol) in THF (10 ml) with ethoxycarbonyl methylide, prepared as described above (3.36 mmol) in THF (6 ml) under reflux for 23 h gave an oil on work-up; p.l.c. (diethyl ether–light petroleum, 2 : 3) afforded two bands. The band of higher R_F gave (4a) (380 mg, 48%) (Found: C, 71.6; H, 6.5. $C_{21}H_{22}O_5$ requires C, 71.2; H, 6.3%); $\nu_{max.}$ 1 720, 1 660, and 1 600 cm^{-1}; δ 1.08 (3 H, t, *J* 8 Hz, CO_2CH_3), 2.8 (1 H, dd, *J* 4.5 and 10 Hz), 3.12 (1 H, dd, *J* 4.5 and 6 Hz), 3.40 (1 H, dd, *J* 6 and 4.5 Hz), 3.78 and 3.87 (6 H, 2 × s, 2 × OMe), 4.05 (2 H, q, *J* 8 Hz, CO_2CH_2), and 6.71—7.90 (8 H, m, ArH). The band of lower R_F gave (4b) (365 mg, 46%); $\nu_{max.}$ 1 720, 1 660, and 1 600 cm^{-1}; δ 1.14 (3 H, t, *J* 8 Hz, $CO_2CH_2CH_3$), 2.56 (1 H, dd, *J* 6 and 10 Hz), 3.02 (1 H, dd, *J* 7 and 10 Hz), 3.31 (1 H, dd, *J* 6 and 7 Hz), 3.81 and 3.85 (6 H, 2 × s, 2 × OMe), 4.12 (2 H, q, *J* 8 Hz, CO_2CH_2), and 6.80—7.81 (8 H, m, ArH); δ_C ($CDCl_3$) 14.10, 29.30, 31.58, 35.15, 55.36, 61.08, 112.41, 114.22, 119.94, 121.17, 127.80, 129.62, 130.08, 138.39, 158.86, 159.89, 169.32, and 193.69.

Ethyl 2-(3,5-Methylenedioxybenzoyl)-3-(2,3,4-trimethoxyphenyl)cyclopropanecarboxylate (12).—Treatment of a solution of the chalcone (11) [2,18,28] (684 mg, 2 mmol) in THF (10 ml) with the ethoxycarbonylmethylide, prepared as described above from ethoxycarbonylmethyl dimethylsulphonium bromide (690 mg, 3 mmol) in THF (5 ml), under reflux for 23 h gave an oil on work-up. P.l.c. (diethyl ether–light petroleum, 1 : 1) gave two main bands. The band of higher R_F gave (12a) (401 mg, 47%) (Found: C, 64.0; H, 5.5. $C_{23}H_{24}O_8$ requires C, 64.5; H, 5.6%); $\nu_{max.}$ 1 720, 1 660, and 1 600 cm^{-1}; δ 1.12 (3 H, t, *J* 7.5 Hz, $CO_2CH_2CH_3$), 2.75 (1 H, dd, *J* 4.5 and 10 Hz), 3.0—3.5 (2 H, m), 3.76 (3 H, s, OMe), 3.87 (6 H, s, 2 × OMe), 6.05 (2 H, s, OCH_2O), and 6.4—7.85 (5 H, m, ArH). The band of lower R_F gave (12b) (412.2 mg, 48%), $\nu_{max.}$ 1 720, 1 660, and 1 600 cm^{-1}; δ 1.21 (3 H, t, *J* 7.5 Hz, $CO_2CH_2CH_3$), 2.60 (1 H, dd, *J* 5.5 and 10 Hz), 3.03 (1 H, dd, *J* 7 and 10 Hz), 3.35 (1 H, dd, *J* 5.5 and 7 Hz), 3.72 and 3.82 (9 H, 2 × s, 3 × OMe), 4.18 (2 H, q, *J* 7.5 Hz, CO_2CH_2), 6.08 (2 H, s, OCH_2O), and 6.3—7.8 (5 H, m, ArH); δ_C ($CDCl_3$) 14.10, 29.76, 31.45, 35.09, 56.14, 60.75, 61.01, 102.07, 105.91, 107.92, 124.94, 131.77, 133.91, 137.29, 148.27, 152.04, 153.53, and 191.54.

1,2,3,4-Tetrahydro-6-methoxy-1-(4-methoxyphenyl)-4-oxonaphthalene-2-carboxylic Acid (6).—To a stirred solution of compound (4a) (250 mg, 0.71 mmol) in benzene (7 ml) was added stannic chloride (0.12 ml, 1.0 mmol) at room temperature under nitrogen. The solution was stirred for 8 h, poured into cold aqueous sodium hydroxide (5%), and extracted with chloroform. The extracts were washed with water, dried (sodium sulphate), and evaporated to afford an oil which was purified by p.l.c. (diethyl ether–light petroleum, 2 : 3) to give the *ester* (5) (201 mg, 80%), m.p. 112—114 °C (MeOH) (Found: C, 71.2; H, 6.3. $C_{21}H_{22}O_5$ requires C, 71.2; H, 6.3%); $\nu_{max.}$ 1 720, 1 680, and 1 600 cm^{-1}; δ 1.03 (3 H, t, *J* 7.5 Hz, $CO_2CH_2CH_3$), 2.88br (2 H, d, *J* 7.5 Hz, $COCH_2$), 3.31 (1 H, m, CO_2CH), 3.81 and 3.88 (6 H, 2 × s, 2 × OMe), 4.03 (2 H, q, *J* 7.5 Hz, CO_2CH_2), 4.59 (1 H, d, *J* 7.5 Hz, ArCH), and 6.81—7.70 (7 H, m, ArH); δ_C ($CDCl_3$) 13.97, 38.53, 46.33, 48.80, 55.23, 55.49, 60.88, 108.83, 114.09, 112.28, 129.88, 130.99, 133.07, 133.78, 136.58, 158.73, 172.70, and 195.50.

Similar treatment of compound (4b) with stannic chloride under the above conditions gave the ethyl ester (5) (78%) identical (i.r., n.m.r., and t.l.c.) with the above described authentic sample.

Hydrolysis of compound (5) as described below for compound (10) gave the acid (6) (90%); $\nu_{max.}$ 3 500—3 000, 1 680, and 1 600 cm^{-1}; δ 2.87 (2 H, d, *J* 7.5 Hz, $COCH_2$), 3.3 (1 H, m, CO_2CH), 3.80 and 3.85 (6 H, 2 × s, 2 × OMe), 4.6 (1 H,

d, *J* 7.5 Hz, ArCH), 6.81—7.70 (7 H, m, ArH), and 8.1br (1 H, s, OH).

Attempted Cyclisation of the Ethyl Cyclopropanecarboxylate (12).—To a stirred solution of (12b) (230 mg, 0.537 mmol) in methylene dichloride (20 ml) was added stannic chloride (0.1 ml, 0.83 mmol) under nitrogen; the reaction mixture was then stirred at room temperature for 3 d. Work-up as above followed by p.l.c. (diethyl ether–light petroleum, 7 : 3) gave two clearly separated bands. The band of lower R_F gave a crystalline *alcohol* (13) (170 mg, 71%), m.p. 129—134 °C (Found: C, 62.1; H, 6.2. $C_{23}H_{26}O_9$ requires C, 61.9; H, 5.9%); $\nu_{max.}$ 3 500, 1 720, 1 670, and 1 600 cm^{-1}; δ 1.15 and 1.20 (3 H, 2 × t, *J* 7 Hz, $CO_2CH_2CH_3$), 3.32 (3 H, m, $COCH_2$ and $CHCO_2$), 3.91 (9 H, s, 3 × OMe), 4.20 (2 H, m, CO_2CH_2), 5.00 and 5.18 (1 H, dd, *J* 3 and 7 Hz, ArCH), 6.09 (2 H, s, OCH_2O), and 6.35—7.72 (5 H, m, ArH). The band of higher R_F gave a mixture of compounds (13) and (14) (50.5 mg, 21%) which with time gave pure (13) identical (i.r., n.m.r., and t.l.c.) with an authentic sample.

Ethyl 1,2,3,4-*Tetrahydro*-6,7-*methylenedioxy*-4-*oxo*-1-(3,4,5-*trimethoxyphenyl*)*naphthalene*-2-*carboxylate* (10a).—To a stirred solution of compound (12) (220 mg, 0.514 mmol) in nitromethane (10 ml) was added freshly distilled boron trifluoride–diethyl ether (0.07 ml, 0.57 mmol) under nitrogen; the reaction mixture was then stirred at room temperature for 15 d. Work-up as described above gave an oil. P.l.c. (diethyl ether–light petroleum, 3 : 2) afforded three bands. The fastest moving band gave the *naphthalene* (20) (18.9 mg, 9%), m.p. 121—123 °C (Found: C, 67.7; H, 5.2. $C_{23}H_{22}O_7$ requires C, 67.3; H, 5.4%); $\nu_{max.}$ 1 710, 1 600, and 1 582 cm^{-1}; δ 1.41 (3 H, t, *J* 7.5 Hz, $CO_2CH_2CH_3$), 3.40 (3 H, s, OMe), 3.98 (3 H, s, OMe), 4.04 (3 H, s, OMe), 4.45 (2 H, q, *J* 7.5 Hz, CO_2CH_2), 6.08 (2 H, s, OCH_2O), 6.92—7.39 (4 H, m, ArH), 7.80 (1 H, d, *J* 2 Hz, ArH), and 8.52 (1 H, d, *J* 2 Hz, ArH).

The second band gave the *naphthodioxole* (10a) (125.5 mg, 57%), m.p. 159—161 °C (MeOH) (lit.,[18] m.p. 162—163 °C) (Found: C, 64.3; H, 6.0. Calc. for $C_{23}H_{24}O_8$: C, 64.4; H, 5.6%); $\nu_{max.}$ 1 720 and 1 670 cm^{-1}; δ 1.10 (3 H, t, *J* 7.5 Hz, $CO_2CH_2CH_3$), 2.92 (2 H, d, *J* 7.5 Hz, $COCH_2$), 3.40 (1 H, m, $CHCO_2$), 3.83 and 3.90 (9 H, 2 × s, 3 × OMe), 4.10 (2 H, q, *J* 7.5 Hz, CO_2CH_2), 4.55 (1 H, d, *J* 7.5 Hz, ArCH), 6.10 (2 H, s, ArH), 6.40 (2 H, s, ArH), 6.55 (1 H, s, ArH), and 7.62 (1 H, s, ArH). The third band afforded the alcohol (13) (22.8 mg, 10%) identical (i.r., n.m.r., and t.l.c.) with the above described authentic specimen.

1,2,3,4-*Tetrahydro*-6,7-*methylenedioxy*-4-*oxo*-1-(3,4,5-*trimethoxyphenyl*)*naphthalene*-2-*carboxylic Acid*.—(10b).—To a suspension of the ester (10a) (428 mg, 1 mmol) in methanol (5 ml) was added aqueous potassium hydroxide (5%; 5 ml). The resulting mixture was then heated under reflux under nitrogen for 3 h. The cooled solution was acidified (10% HCl) and extracted with chloroform. The extracts were washed with water, dried (sodium sulphate), and evaporated to yield an almost colourless solid of the *acid* (10b) (406 mg, 95%), m.p. 219—221 °C (recrystallised from methanol) (lit.,[18] m.p. 219—220 °C, 220—222 °C [13]); $\nu_{max.}$ 3 500—3 000, 1 680, and 1 600 cm^{-1}; δ 2.85 (2 H, d, *J* 7.5 Hz, $COCH_2$), 3.38 (1 H, m, $CHCO_2$), 3.79 (6 H, s, 2 × OMe), 3.84 (3 H, s, OMe), 4.61 (1 H, d, *J* 7.5 Hz, ArCH), 6.08 (2 H, s, OCH_2O), 6.38 (2 H, s, ArH), 6.52 (1 H, s, ArH), 7.0br (1 H, s, OH, replacement + D_2O), and 7.59 (1 H, s, ArH).

Aldol Hydroxymethylation: General Procedure.—A solution of the tetralone in aqueous base was treated with the indicated formaldehyde at room temperature under nitrogen. The reaction solution was stirred at room temperature for the time period indicated, and was then acidified with chloroform. The extracts were washed with water, saturated sodium hydrogen carbonate solution, and water and dried (brine, sodium sulphate), and evaporated. P.l.c. or recrystallisation of the residue gave the pure product.

3-*Hydroxymethylpicropodophyllone* (1,3,3a,4,9,9a-*Hexahydro*-3a-*hydroxymethyl*-6,7-*methylenedioxy*-9-(3,4,5-*trimethoxyphenyl*)*naphtho*[2,3-c]*furan*-1,4-*dione*) (26).—This compound was prepared as described above from (10b). P.l.c. (diethyl ether–light petroleum, 3 : 2) of the crude product gave compound (26),[13] m.p. 108—110 °C (benzene) (lit.,[13] m.p. 109—111 °C) (Found: C, 62.5; H, 5.0. Calc. for $C_{23}H_{22}O_9$: C, 62.4; H, 4.9%); $\nu_{max.}$ 3 450, 1 725, 1 675, and 1 600 cm^{-1}; δ 3.15—3.7 (3 H, m), 3.78 (6 H, s, 2 × OMe), 3.84 (3 H, s, OMe), 4.51 (2 H, q of AB, *J* 10 Hz), 4.84br (1 H, s, ArCH), 6.15 (2 H, s, OCH_2O), 6.24 (2 H, s, ArH), 6.79 (1 H, s, ArH), and 7.55 (1 H, s, ArH); δ_C ($CDCl_3$) 42.88, 47.95, 54.19, 56.33, 60.95, 64.06, 72.71, 102.40, 105.19, 106.36, 109.74, 127.35, 137.36, 138.07, 138.85, 148.66, 153.66, 154.05, 176.21, and 196.87.

1,3,3a,4,9,9a-*Hexahydro*-4-*hydroxy*-3a-*hydroxymethyl*-6-*methoxy*-9-(4-*methoxyphenyl*)-*naphtho*[2,3-c]*furan*-1-*one* (23).—This compound was prepared as described above, $\nu_{max.}$ 3 450, 1 760, and 1 680 cm^{-1}; δ 3.0—3.7 (3 H, m), 3.75br (3 H, s, OMe), 3.83 (3 H, s, OMe), 4.19br (1 H, s), 4.53br (1 H, s), 4.80 (1 H, s), and 6.60—7.51 (7 H, m, ArH) δ_C ($CDCl_3$) 44.51, 49.18, 49.51, 55.36, 68.87, 70.43, 70.69, 110.56, 111.70, 113.68, 127.28, 128.26, 130.27, 133.13, 139.43, 158.34, 159.64, and 179.48.

A solution of compound (23) (50 mg) in acetone (5 ml) was treated with a slight excess of Jones reagent at 0 °C for 4—5 min. Methanol was added to the mixture and the green solution was warmed to room temperature. Water was then added and the acetone was evaporated. The aqueous residue was then extracted well with chloroform. The chloroform extracts were washed successively with water, saturated aqueous sodium hydrogen carbonate, and water, and then dried (sodium sulphate) and concentrated. P.l.c. (diethyl ether–light petroleum, 1 : 1) gave the corresponding tetralone as an *oil* (35 mg, 70%); $\nu_{max.}$ 3 400, 1 780, 1 680, and 1 600 cm^{-1}; δ 3.3—3.6 (3 H, m), 3.80 (3 H, s, OMe), 3.90 (3 H, s, OMe), and 4.10—4.9 (4 H, m).

1,3,3a,4,9,9a-*Hexahydro*-3a-*hydroxymethyl*-6,7-*dimethoxy*-9-(3,4-*methylenedioxyphenyl*)*naphtho*[2,3-c]*furan*-1,4-*dione* (25).—Compound (25) was prepared as described above from (22); it had m.p. 241—243 °C (methylene dichloride–benzene) (Found: C, 63.2; H, 4.8. $C_{22}H_{20}O_8$ requires C, 64.0; H, 4.9%); $\nu_{max.}$ 3 490, 1 775, 1 660, and 1 600 cm^{-1}; δ [$(CD_3)_2SO$] 3.1—3.5 (3 H, m), 3.80 and 3.85 (6 H, 2 × s, 2 × OMe), 4.41—4.55 (2 H, m), 4.75 (1 H), 6.01 (2 H, s, OCH_2O), and 6.11—7.50 (5 H, m, ArH); δ_C[$(CD_3)_2SO$] 43.73, 45.42, 54.90, 55.49, 56.01, 60.23, 71.08, 101.03, 107.92, 108.57, 111.04, 112.02, 121.11, 125.20, 136.77, 137.16, 145.99, 147.55, 148.79, 154.83, 176.21 (lactone), and 195.50 (ketone).

1,3,3a,4,9,9a-*Hexahydro*-4-*hydroxy*-3a-*hydroxymethyl*-6,7-*dimethoxy*-9-(3,4-*methylenedioxyphenyl*)*naphtho*[2,3-c]*furan*-1-*one* (24).—This compound was prepared from compound (22) as described above (Found: C, 62.9; H, 5.5. $C_{22}H_{22}O_3$ requires C, 63.7; H, 5.3%); $\nu_{max.}$ 3 450, 1 760, 1 670, and 1 600 cm^{-1}; δ 3.5—3.76 (3 H, m), 3.83 (3 H, s), 3.94 (3 H, s), 4.23br (1 H, s), 4.52 (1 H, m), 4.83br (1 H, s), 6.0 (2 H, s), and 6.5—7.71 (5 H, m); δ_C ($CDCl_3$) 45.22, 49.45, 49.64,

56.01, 63.87, 69.26, 70.37, 101.16, 107.79, 108.25, 108.44, 112.34, 120.33, 126.96, 130.08, 135.08, 136.58, 148.07, 148.42, 148.79, and 178.74 (lactone).

Oxidation of compound (24) with Jones reagent (0 °C, 5 min), as previously described for compound (23), gave compound (25) (71%) identical (i.r., m.p., and t.l.c.) with the above known specimen.

Picropodophyllone (1,3,3a,4,9,9a-*Hexahydro*-6,7-*methylenedioxy*-9-(3,4,5-*trimethoxyphenyl*)*naphtho*[2,3-c]*furan*-1,4-*dione* (9).[13]—An excess of Jones reagent was added to a solution of compound (26) (40 mg) in acetone (20 ml) and the mixture was stirred for 50 min. Methanol was then added to it and the whole diluted with water and extracted with chloroform. The extracts were washed with water, saturated with sodium hydrogen carbonate, dried (brine, sodium sulphate), and evaporated. P.l.c. (diethyl ether–light petroleum, 7 : 3) of the crude oil gave picropodophyllone (9) (26.9 mg, 72%); $\nu_{max.}$ 1 770, 1 680, and 1 600 cm^{-1}; δ 3.31 (1 H, d, *J* 3 Hz), 3.80 (6 H, s, 2 × OMe), 3.83 (3 H, s, OMe), 4.10—4.91 (4 H, m), 6.05 (2 H, s, OCH_2O), 6.25 (2 H, s, ArH), 6.70 (1 H, s, ArH), and 7.50 (1 H, s, ArH). The synthetic and natural picropodophyllone were indistinguishable by t.l.c. in a variety of solvent systems (SiO_2): $CHCl_3$–ethyl acetate, 4 : 1; benzene–ethyl acetate, 3 : 2; CH_2Cl_2–acetone, 7 : 1; CH_2Cl_2–acetone, 4 : 1; $CHCl_3$.

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