Total Syntheses of Riccardins A, B, and C, Cytotoxic Macrocyclic Bis(bibenzyls) from Liverworts[1]

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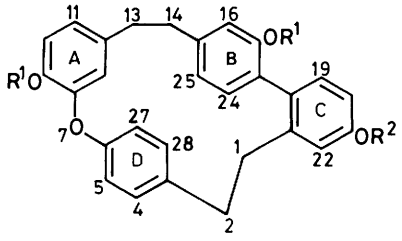
Di-*O*-methylriccardin A (**3**), riccardin A (**1**), and riccardin B (**4**) were synthesized by convergent schemes. Rings A and D of both riccardin A and B, as well as rings B and C of riccardin B were joined by the Ullmann ether synthesis. The aryl-aryl bond in riccardin A was established by Ni(0)-assisted intramolecular coupling of a di-iodoester (**17**). Rings A and B were linked in all syntheses by the Wittig reaction, whereas ring closure was effected by a tetraphenylethene catalyzed Wurtz reaction. Demethylation of (**3**) gave riccardin C (**2**).

Liverwort species are a rich source of terpenoids, phenolics, lipids, *etc.*[2] Among the phenolic components, macrocyclic bis(bibenzyls) containing two Ar–O–Ar bonds or one Ar–O–Ar and one Ar–Ar bond are of interest both from a biogenetic and a synthetic point of view, and some of them have been reported to exhibit cytotoxic acitivity against KB cells and P388 lympholytic leukemia.[3] Since the isolation of riccardin A (**1**) and B (**4**) from *Riccardia multifida*[4] the number of macrocyclic bis(bibenzyls) found in liverwort species has risen to at least 17, representing 7 different frameworks with 16-, 18-, and 20-membered rings.[5–10] It is of interest that all of them can be derived by oxidative cyclization of a single precursor (**7**) involving the positions indicated by arrows, combined with biochemical oxygenations and *O*-methylations. In fact, such open-chain candidates for oxidative cyclization, the perrottetins [*e.g.* perrottetin E (**7**)] have recently been discovered in a liverwort.[11,12]

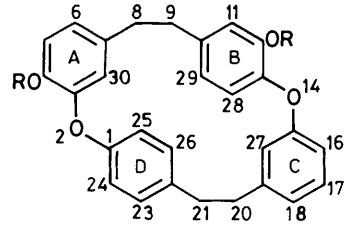
Our interest in the synthesis of riccardins was motivated by the challenge of constructing the unsymmetrical biphenyl moiety in riccardin A and by the fact that the structure of riccardin B had not been fully elucidated by Asakawa *et al.*[4] It remained unsettled whether the bibenzyl units were linked up as in (**4**) or by an ethano bridge between the C and D rings at C-18 and C-26.[4] The present and other syntheses[13,14] clarified this problem.

First, the synthesis of riccardin B was completed[13] and experience thus gained was exploited for the synthesis of riccardin A dimethyl ether and finally of riccardin A itself.

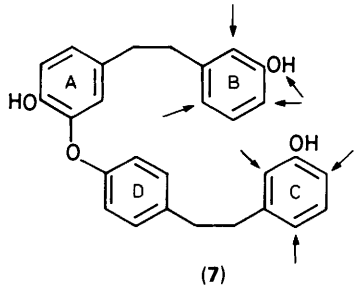
An unambiguous and convergent synthesis of riccardin B required the preparation of two diaryl ether building blocks representing the A,D and B,C diaryl ether units with different functional groups on each of the aryl rings, permitting a controlled coupling of the two units at a later stage (Scheme). Accordingly the ester aldehydes (**8**) and (**12**) were prepared from known components using the Ullmann ether synthesis.† Since (**8**) was more accessible than (**12**), the former was transformed in three steps into the phosphonium salt (**11**).



(**1**) R^1 = H, R^2 = Me (riccardin A)
(**2**) R^1 = R^2 = H (riccardin C)
(**3**) R^1 = R^2 = Me



(**4**) R = H (riccardin B)
(**5**) R = Me
(**6**) R = Ac

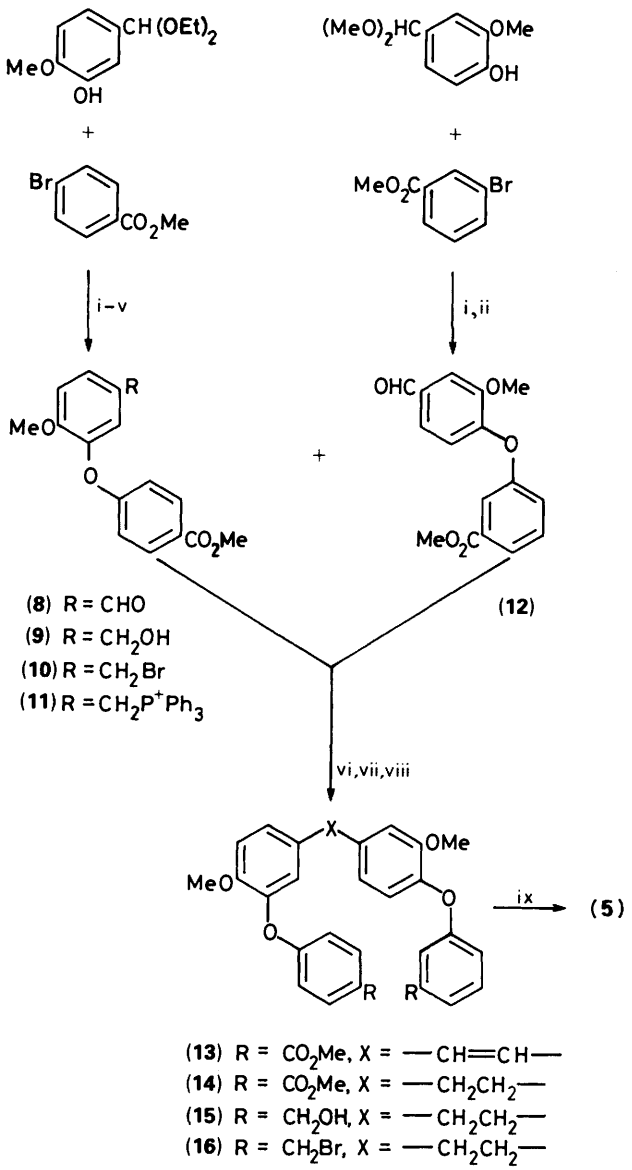


(**7**)

Wittig reaction of (**11**) and (**12**) afforded a mixture of *E*- and *Z*-olefins (**13**). This was converted by hydrogenation,‡ reduction

† The alternative way, *i.e.* reaction of 4-bromo-3-methoxybenzaldehyde dimethyl acetal and methyl 3-hydroxybenzoate, gave (**12**) in negligible yield.

‡ To ensure that the catalyst should not be deactivated, water should be strictly avoided during the work up of (**11**).



(13) R = CO_2Me, X = —CH=CH—
(14) R = CO_2Me, X = —CH_2CH_2—
(15) R = CH_2OH, X = —CH_2CH_2—
(16) R = CH_2Br, X = —CH_2CH_2—

Scheme. *Reagents*: i, CuO, C_5H_5N, 120 °C; ii, H^+; iii, $NaBH_4$; iv, HBr, water–C_6H_6; v, Ph_3P–MeCN, heat; vi, NaOMe; vii, H_2/Pd–C; viii, PBr_3; ix, Na, $Ph_2C{=}CPh_2$

with lithium aluminium hydride, and treatment with PBr_3 to the dibromide (**16**), which was cyclized to (**5**) by tetraphenylethene radical anion.[15] Riccardin B dimethyl ether (**5**) was obtained as the only isolable product in modest yield. It was demethylated with boron tribromide to riccardin B (**4**) which was characterized as the diacetate (**6**).

Since the substitution pattern of the A and D rings was identical in riccardins A and B, the key intermediate in the synthesis of the former was a suitably functionalized unsymmetrical biphenyl. This was prepared by Ni(0)$(Ph_3P)_4$ assisted coupling[16] of the di-iodo ester (**17**), which gave the lactone (**19**) in 17% yield. The main reaction was selective deiodination of the aldehyde component of (**17**) to give the monoiodo ester (**18**). Despite a recent observation,[17] addition of potassium iodide did not improve the yield of (**19**).

The two key intermediates, (**19**) and (**11**), were joined by the Wittig reaction, and the product (**25**) was hydrogenated to give (**26**) which was reduced with lithium aluminium hydride to give a triol (**29**). The phenolic hydroxyl of (**29**) was methylated with diazomethane to yield the diol (**30**). Treatment of (**30**) with phosphorus tribromide gave a dibromide (**31**) which was finally cyclized to di-*O*-methylriccardin A (**3**). Demethylation of (**3**) with boron tribromide in methylene dichloride gave riccardin C (**2**).

The synthesis of riccardin A itself required an A,D ring intermediate with a protected free hydroxy group. This could be readily prepared by selective demethylation of (**8**) with aluminium chloride followed by benzylation, reduction, hydroxybromo replacement and transformation to the triphenylphosphonium salt [*via* the sequence (**8**) ⟶ (**20**) ⟶ (**21**) ⟶ (**22**) ⟶ (**23**) ⟶ (**24**)].

Wittig reaction of the building blocks (**24**) and (**19**) gave the olefin (**27**), which was hydrogenated, reduced with lithium aluminium hydride, selectively rebenzylated at the aromatic hydroxy groups and finally converted into the dibromide [(**23**) ⟶ (**28**) ⟶ (**32**) ⟶ (**33**) ⟶ (**34**)]. Wurtz reaction of (**34**) was accompanied by partial and total debenzylation and therefore the crude product was directly debenzylated to yield riccardin A (**1**).

The identity of synthetic and natural products was established by mass spectrometry and ^1H n.m.r. spectroscopy at 400 MHz. An authentic sample was not available.

An interesting feature of the n.m.r. spectrum of (**33**) and (**34**) is the pronounced broadening of the signal for the ethylene bridge protons. Line broadening of certain signals was even more conspicuous in the spectrum of di-*O*-methylriccardin A (**3**). Thus at room temperature 4-H, 5-H, 27-H, and 28-H formed an ABCD-system, while protons of the ethylene bridges gave, even at 400 MHz, a rather unstructured band of overlapping multiplets at 2.60—3.15 p.p.m. At 100 °C in $(CD_3)_2SO$ the ABCD-system simplifed to an AA'BB'-system, while the ethylene bridge protons gave two sharp singlets at 2.83 and 2.92 p.p.m. All this indicated moderately hindered rotation of the *p*-disubstituted benzene ring and restricted mobility of the whole ring system.

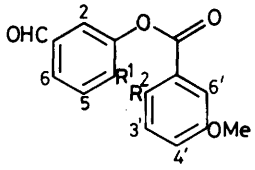
In the mass spectrum of (**3**), formation of the second most abundant ion (*m/z* 239, 53%) can be interpreted by fission of the molecular ion across the ethylene bridges coupled with migration of a hydrogen atom from the BC-half to the AD-half of the molecule. In fact no ion of *m/z* 226 could be detected while one at *m/z* 227 was fairly intense (12%).

Experimental

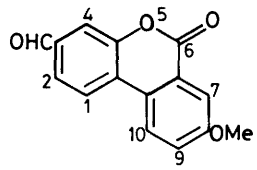
Evaporations were carried out under reduced pressure. For chromatography, silica gel (Merck 60) was used. ^1H N.m.r. spectra were recorded in deuteriochloroform with TMS as internal standard on Varian XL 100, XL 400, and Perkin-Elmer R12 instruments (at 400, 100, and 60 MHz, respectively). Mass spectra were taken on a JEOL 0156-2 double focus instrument.

3-Hydroxy-4-methoxybenzaldehyde Diethyl Acetal.—3-Hydroxy-4-methyoxybenzaldehyde (7.6 g, 0.05 mol) was stirred for 24 h with triethyl orthoformate (9.0 g, 0.06 mol), EtOH (2 ml), and dry NH_4NO_3. After addition of triethylamine (0.1 ml), the solution was evaporated to give the acetal as an oil (10.8 g, 96%); δ 1.18 (6 H, t, *J* 7 Hz, CH_2CH_3), 3.48 (4 H, q, *J* 7 Hz, CH_2), 3.85 (3 H, s, OMe), 5.33 (1 H, s, CH), 6.05 (1 H, s, 2-H), 6.8—7.0 (2 H, m, 5- and 6-H).

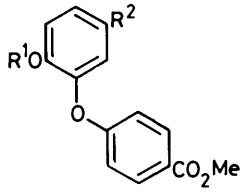
4-Methoxy-3-(4-methoxycarbonylphenoxy)benzaldehyde (**8**). —Methyl 4-bromobenzoate (8.2 g, 40 mmol), 3-hydroxy-4-methoxybenzaldehyde diethyl acetal (13.6 g, 50 mmol), CuO (0.5 g, 6.3 mmol), and K_2CO_3 (6.9 g, 50 mmol) in dry pyridine (70 ml) were stirred under argon for 48 h under reflux. The mixture was diluted with EtOAc (250 ml), filtered, and the filtrate stirred slowly first with 20% aqueous H_2SO_4 for 2 h and



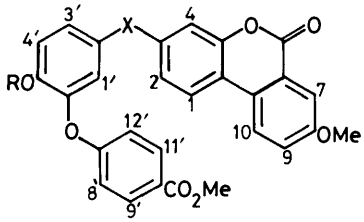
(17) $R^1 = R^2 = I$
(18) $R^1 = H, R^2 = I$



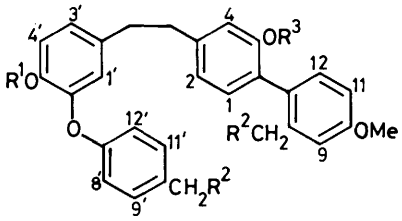
(19)



(20) $R^1 = H, R^2 = CHO$
(21) $R^1 = CH_2Ph, R^2 = CHO$
(22) $R^1 = CH_2Ph, R^2 = CH_2OH$
(23) $R^1 = CH_2Ph, R^2 = CH_2Br$
(24) $R^1 = CH_2Ph, R^2 = CH_2P^+Ph_3.Br^-$



(25) R = Me, X = —CH=CH—
(26) R = Me, X = —CH_2CH_2—
(27) R = CH_2Ph, X = —CH=CH—
(28) R = H, X = —CH_2CH_2—



(29) R^1 = Me, R^2 = OH, R^3 = H
(30) $R^1 = R^3$ = Me, R^2 = OH
(31) $R^1 = R^3$ = Me, R^2 = Br
(32) $R^1 = R^3$ = H, R^2 = OH
(33) $R^1 = R^3 = CH_2Ph$, R^2 = OH
(34) $R^1 = R^3 = CH_2Ph$, R^2 = Br

then 5% aqueous NaOH (4 × 50 ml). The upper phase was dried and evaporated, and the residue was extracted several times with boiling hexane–acetone (5:1). On cooling the product (3.4 g, 30%) crystallized from the extract; m.p. 116—118 °C (from methanol) (Found: C, 67.0; H, 5.1. $C_{16}H_{14}O_5$ requires C, 67.1; H, 4.9%); δ 3.96 and 3.98 (2 × 3 H, 2 × s, OMe), 6.90 (2 H, d, *J* 8.5 Hz, 2′- and 6′-H), 7.12 (1 H, d, *J* 8.5 Hz, 5-H), 7.57 (1 H, d, *J* 2.5 Hz, 2-H), 3.72 (1 H, dd, *J* 8.5 and 2.5 Hz, 6-H), 7.97 (2 H, d, *J* 8.5 Hz, 3′- and 5′-H), 9.83 (1 H, s, CHO).

Methyl 4-(5-*Hydroxymethyl*-2-*methoxyphenoxy*)*benzoate* (**9**).—To a stirred suspension of (**8**) (1.14 g, 4 mmol) in EtOH (10 ml), $NaBH_4$ (103 mg, 2.72 mmol) was added. After 1 h the solution was acidified with AcOH, evaporated, and the residue triturated with water and extracted with CH_2Cl_2 to give (**9**) (100 mg, 90%), m.p. 76—79 °C (from Et_2O) (Found: C, 66.9; H, 5.5. $C_{16}H_{16}O_5$ requires C, 66.7; H, 5.6%); δ 2.02 (1 H, s, OH), 3.76 and 3.88 (2 × 3 H, 2 × s, OMe), 4.60 (2 H, s, CH_2), 6.91 (2 H, d, *J* 9 Hz, 3- and 5-H), 6.99 (1 H, d, *J* 8.3 Hz, 5′-H), 7.09 (1 H, d, *J* 1.7 Hz, 2′-H), 7.19 (1 H, dd, *J* 8.3 and 1.7 Hz, 6′-H), 7.97 (2 H, d, *J* 9 Hz, 2- and 6-H).

4-*Methoxy*-3-(4-*methoxycarbonylphenoxy*)*benzyltriphenylphosphonium Bromide* (**11**).—A solution of (**9**) (1.0 g, 3.47 mmol) in C_6H_6 (12 ml) was stirred vigorously for 1 h with 47% aqueous HBr (6 ml). The organic layer was extracted with aqueous $NaHCO_3$ and water and then evaporated. To the residue MeCN (9 ml) and Ph_3P (1.27 g, 4.84 mmol) was added and the mixture boiled for 1 h. Evaporation and treatment of the residue with hot C_6H_6 gave (**11**) (1.64 g, 76%), m.p. 210—211 °C (Found: C, 66.3; H, 4.8; Br, 12.8. $C_{34}H_{30}BrPO_4$ requires C, 66.6; H, 4.9; Br, 13.0%).

3-*Methoxy*-4-(3-*methoxycarbonylphenoxy*)*benzaldehyde* (**12**).—Methyl 3-bromobenzoate (8.6 g, 40 mmol) and vanillin dimethylacetal[18] (9.9 g, 50 mmol) were reacted as described for (**8**). The crude product was chromatographed on silica gel (eluant C_6H_6–butan-2-one, 20:1) to yield (**12**) as a resin (2.1 g, 18%) which slowly crystallized; m.p. 60—62 °C (Found: C, 67.2; H, 4.7. $C_{16}H_{14}O_5$ requires C, 67.1; H, 4.9%); δ 3.94 and 3.91 (2 × 3 H, 2 × s, OMe), 7.03 (1 H, d, *J* 8.0 Hz, 5-H), 7.23 (1 H, ddd, *J* 8.1, 2.4, and 1.3 Hz, 6′-H), 7.43 (1 H, ddd, *J* 8.1, 7.5, and 0.6 Hz, 5′-H), 7.45 (1 H, dd, *J* 8.0 and 1.8 Hz, 6-H), 7.57 (1 H, d, *J* 1.8 Hz, 2-H), 7.67 (1 H, ddd, *J* 2.4, 1.5, and 0.6 Hz, 2′-H), 7.85 (1 H, ddd, *J* 7.5, 1.5, and 1.3 Hz, 4′-H), 9.96 (1 H, s, CHO).

(E)- *and* (Z)-1-[3-*Methoxy*-4-(3-*methoxycarbonylphenoxy*)*phenyl*]-2-[4-*methoxy*-3-(4-*methoxycarbonylphenoxy*)*phenyl*]-*ethene* (**13**).—To a solution of (**11**) (1.23 g, 2 mmol) in dry MeOH (6 ml) first 1M NaOMe (2.4 ml) and then a solution of (**12**) (0.572 g, 2 mmol) in dry MeOH (4 ml) was added. After 1 h, C_6H_6 (20 ml) was added and the solution was filtered through a short column of silica gel. The column was washed with C_6H_6, and evaporation of the combined fractions gave a mixture of olefins (0.6 g, 55%) (Found: C, 70.9; H, 5.4. $C_{32}H_{28}O_8$ requires C, 71.1; H, 5.2%); δ 3.62, 3.77, 3.84, and 3.81 (total intensity 12 H, OMe), 6.55 (0.9 H, s, (*Z*) CH=CH), 7.10 (s, (*E*) CH=CH), 6.80—8.1 (*ca.* 15 H, m, Ar-H).

1-[3-*Methoxy*-4-(3-*methoxycarbonylphenoxy*)*phenyl*]-2-[4-*methoxy*-3-(4-*methoxycarbonylphenoxy*)*phenyl*]*ethane* (**14**).—Hydrogenation of (**13**) in ethyl acetate–methanol (5:30) over palladium-charcoal gave, after the usual work-up, (**14**) as a resin in quantitative yield (Found: C, 70.6; H, 5.4. $C_{32}H_{30}O_8$ requires C, 70.8; H, 5.6%); δ 2.88 (4 H, s, CH_2CH_2), 3.71 and 3.73 (2 × 3 H, 2 × s, OMe), 3.86 (6 H, s, OMe), 6.6—8.1 (14 H, m, Ar-H).

1-[3-(4-*Hydroxymethylphenoxy*)-4-*methoxyphenyl*]-2-[4-(3-*hydroxymethylphenoxy*)-3-*methoxyphenyl*]*ethane* (**15**).—To a solution of (**14**) (0.54 g, 1.0 mmol) in THF (10 ml), $LiAlH_4$

(0.1 g, 2.6 mmol) was added. After 1 h, Et_2O (20 ml) was added and the reducing agent was decomposed with EtOAc and then with 20% aqueous H_2SO_4. Evaporation of the solvent gave (**15**) as an oil (0.48 g, 87%) (Found M^+ 486. $C_{30}H_{30}O_6$ requires 486); δ 1.97 (2 H, br s, OH), 2.85 (4 H, s, CH_2CH_2), 3.72 and 3.78 (2 × 3 H, s, OMe), 4.62 (4 H, s, CH_2), 6.6—7.4 (14 H, m, Ar-H).

1-[3-(4-*Bromomethylphenoxy*)-4-*methoxyphenyl*]-2-[4-(3-*bromomethylphenoxy*)-3-*methoxyphenyl*]*ethane* (**16**).—A solution of (**15**) (0.35 g, 0.72 mmol) and PBr_3 (0.24 g, 0.88 mmol) in benzene (3.3 ml) were heated for 1 h at 80 °C. After washing with water and aqueous $NaHCO_3$, evaporation of the organic layer gave (**16**) as an oil in quantitative yield (Found: M^+ 610, 612, 614. $C_{30}H_{28}Br_2O_4$ requires 610, 612, 614); δ 2.90 (4 H, s, CH_2CH_2), 3.75 and 3.79 (2 × 3 H, s, OMe), 4.42 and 4.48 (2 × 2 H, s, CH_2Br), 6.70—7.4 (14 H, m, Ar-H).

Di-O-methylriccardin B (**5**).—Sodium (43 mg, 1.9 mmol) was dissolved in a solution of tetraphenylethene (315 mg, 0.95 mmol) in THF (10 ml). To the resulting deep purple solution, (**16**) (147 mg, 0.24 mmol) in THF (10 ml) was added dropwise over 8 h. After standing overnight the mixture was quenched with MeOH, evaporated and the residue purified by preparative t.l.c. (eluant C_6H_6–EtOAc, 8:1) to give (**5**) (30 mg, 27%), m.p. 150—152.5 °C (from EtOH) (lit.,[4] m.p. 151—152.5 °C); δ(400 MHz) 2.78 and 2.81 (2 × 4 H, 2 × s, CH_2CH_2), 3.79 and 3.86 (2 × 3 H, 2 × s, OMe), 5.98 (1 H, dd, *J* 2.4 and 1.5 Hz, 27-H), 6.00 (1 H, dd, *J* 8.1 and 2.0 Hz, 29-H), 6.02 (1 H, d, *J* 2.1 Hz, 30-H), 6.16 (1 H, d, *J* 8.1 Hz, 28-H), 6.59 (2 H, d, *J* 8.5 Hz, 24- and 25-H), 6.66 (1 H, d, *J* 2.0 Hz, 11-H), 6.71 (2 H, d, *J* 8.5 Hz, 23- and 26-H), 6.94 (1 H, d, *J* 8.2 Hz, 5-H), 6.95 (1 H, ddd, *J* 8.0, 2.4, and 1.0 Hz, 16-H), 7.01 (1 H, dd, *J* 8.2 and 2.1 Hz, 6-H), 7.05 (1 H, ddd, *J* 7.6, 1.5, and 1.0 Hz, 18-H), 7.32 (1 H, dd, *J* 8.0 and 7.6 Hz, 17-H) [lit.,[4] δ 2.77 (s), 2.80 (s), 3.77 (s), 3.85 (s), 5.98 (dd), 5.99 (dd), 6.02 (d), 6.17 (d), 6.59 (dd), 6.66 (d), 6.71 (d), 6.94 (d), 6.95 (ddd), 7.00 (dd), 7.04 (ddd), 7.31 (dd)].

Riccardin B Diacetate (**6**).—To a solution of (**5**) (45 mg, 0.1 mmol) in CH_2Cl_2 (5 ml) cooled to −78 °C were added five drops of BBr_3. After 1 h the solution was allowed to warm to room temperature and ice was added. The organic phase was evaporated and the residue acetylated with Ac_2O–pyridine. The usual work-up and crystallization from EtOH gave (**6**) (30 mg, 60%), m.p. 159—162 °C (lit.,[4] 148—149 °C); δ(400 MHz) 2.16 and 2.20 (2 × 3 H, s, OAc), 2.81 and 2.82 (2 × 4 H, s, CH_2CH_2), 6.04 (1 H, t, *J* 2.0 Hz, 27-H), 6.17 (1 H, d, *J* 2.0 Hz, 30-H), 6.36 (1 H, dd, *J* 8.3 and 1.8 Hz, 29-H), 6.38 (1 H, d, *J* 8.3 Hz, 28-H), 6.65 and 6.73 (2 × 2 H, AA′BB′-system, *J* 8.5 Hz, 23-, 24-, 25-, and 26-H), 6.80 (1 H, d, *J* 1.8 Hz, 11-H), 6.95 (1 H, dd, *J* 8.0, 2.5 and 1.0 Hz, 16-H), 7.04 (1 H, dd, *J* 8.3 and 2.0 Hz, 6-H), 7.06 (1 H, ddd, *J* 7.5, 1.6, and 1.0 Hz, 18-H), 7.11 (1 H, d, *J* 8.3 Hz, 5-H), 7.33 (1 H, dd, *J* 8.0 and 7.5 Hz, 17-H).

3-*Hydroxy*-4-*iodobenzaldehyde*.—To a stirred solution of $SnCl_2 \cdot 2H_2O$ (13.4 g, 59.6 mmol) in 37% aqueous HCl (64 ml) cooled to 5 °C, 3-hydroxy-4-nitrobenzaldehyde[19] (3.2 g, 19.1 mmol) was added. After 25 min the solution was heated for 20 min on a steam bath, then cooled in an ice bath, and treated with $NaNO_2$ (1.34 g, 19.4 mmol) in water (5 ml) and then with a solution of NaI (6.4 g, 38 mmol) in 2.5M aqueous H_2SO_4. Stirring was continued for 24 h followed by heating to 100 °C for 10 min. The sticky product was separated, left to dry in air, pulverized, filled into a column and extracted with CH_2Cl_2. The combined extracts were shaken with dilute aqueous $NaHSO_3$, evaporated and the residue recrystallized from C_6H_6 to give the product (1.0 g, 20%), m.p. 126—128 °C (Found: C, 34.0; H, 2.0; I, 50.7. $C_7H_5IO_2$ requires C, 33.9; H, 2.0; I, 51.2%); δ 5.87 (1 H, s, OH), 7.15 (1 H, dd, *J* 8 and 2 Hz, 6-H), 7.43 (1 H, d, *J* 2 Hz, 2-H), 7.88 (1 H, d, *J* 8 Hz, 5-H), 9.9 (1 H, s, CHO).

4-*Iodo*-3-(2-*iodo*-5-*methoxybenzoyloxy*)*benzaldehyde* (**17**).—2-Iodo-5-methoxybenzoic acid[20] (5.56 g, 2.0 mmol) was boiled with $SOCl_2$ (14 ml) for 1 h. Excess reagent was evaporated, then C_6H_6 (2 × 30 ml) was distilled off from the residue and the resulting acid chloride was dissolved in pyridine (17 ml). 3-Hydroxy-4-iodobenzaldehyde (4.96 g, 2.0 mmol) was added and the mixture stirred for 24 h. The solution was poured into 10% aqueous sulphuric acid (170 ml), and the precipitate was filtered off, dried, and stirred with boiling methanol (50 ml) for 20 min to give (**17**) (10.1 g, 63%), m.p. 137—139 °C (Found: C, 35.5; H, 2.0; I, 49.0. $C_{15}H_{10}I_2O_4$ requires C, 35.5; H, 2.0; I, 50.0%); δ 3.82 (3 H, s, OMe), 6.81 (1 H, dd, *J* 9 and 2.5 Hz, 4′-H), 7.25 (1 H, dd, *J* 8 and 2 Hz, 6-H), 7.70 (1 H, d, *J* 2.5 Hz, 6′-H), 7.80 (1 H, d, *J* 2 Hz, 2-H), 7.90 (1 H, d, *J* 9 Hz, 3′-H), 8.03 (1 H, d, *J* 8 Hz, 5-H), 9.93 (1 H, s, CHO).

8-*Methoxy*-6-*oxodibenzo*[bd]*pyran*-3-*carbaldehyde* (**19**).—$NiCl_2(Ph_3P)_2$[21] (32.5 g, 50 mmol), Ph_3P (26.05 g, 100 mmol) and Zn powder (3.9 g, 55 mmol) in freshly distilled DMF (100 ml) were stirred under argon at 55 °C for 1 h, after which (**17**) (10.42 g, 20.6 mmol) was added. After 18 h the starting material disappeared. The mixture was poured into 5% aqueous HCl (600 ml), and the precipitate was chromatographed on silica gel with benzene to give first the iodoester (**18**) (2.35 g, 30%) as an oil* and the desired lactone (**19**) (0.89 g, 17%) as yellow cubes, m.p. 228—234 °C (transformation at *ca.* 200 °C) (Found: C, 70.7; H, 4.0. $C_{15}H_{10}O_4$ requires C, 70.9; H, 4.0%); $\nu_{max.}$ 1 750, 1 695 cm^{-1}; δ_H [$CDCl_3$–$(CD_3)_2SO$; 400 MHz) 3.97 (3 H, s, OMe), 7.49 (1 H, dd, *J* 8.8 and 2.8 Hz, 9-H), 7.78 (1 H, d, *J* 2.8 Hz, 7-H), 7.80 (1 H, d, *J* 1.7 Hz, 4-H), 7.85 (1 H, dd, *J* 8.2 and 1.7 Hz, 2-H), 8.24 (1 H, d, *J* 8.8 Hz, 10-H), 8.26 (1 H, d, *J* 8.2 Hz, 1-H); δ_C 55.43 (Me), 111.36 (C-7), 117.83 (C-9), 122.60 and 122.95 (C-10a, C-10b), 123.04 (C-4), 123.51 (C-2), 124.58 and 124.64 (C-1, C-10), 126.10 (C-6a), 136.03 (C-3), 149.84 (C-4a), 159.69 (C-8), 160.64 (C-6), 190.45 (CHO); *m/z* 255 (15%), 254 (M^+, 100), 253 (28), 239 (11), ($M^+ - CH_3$), 197 (9), 155 (10), 127 (8), 126 (12).

8-*Methoxy*-3-{2-[4-*methoxy*-3-(4-*methoxycarbonylphenoxy*)-*phenyl*]*ethyl*}*dibenzo*[bd]*pyran*-6-*one* (**26**).—To (**11**) (930 mg, 1.5 mmol) and (**18**) (320 mg, 1.25 mmol) in dry CH_2Cl_2 (15 ml) was added 1M NaOMe (1.7 ml). After 1 h the mixture was filtered through a column of silica gel and the product (**25**) (*E*:*Z* *ca.* 2:1) was eluted with hexane–acetone (5:1); δ 3.7—4.0 (9 H, 6 × s, OMe), 6.8—8.1 (15 H, m, Ar-H). The mixture of *E* and *Z* olefins was hydrogenated in MeOH–EtOAc (1:1) over Pd–charcoal catalyst to give, after the usual work-up, (**26**) (356 mg, 55%) as an oil (Found: M^+, 510. $C_{31}H_{26}O_7$ requires M^+, 510); *m/z* 511 (10%), 510 (M^+, 25), 272 (19), 271 (100), 240 (3), 239 (17), 212 (3), 197 (6).

1-[4-(2-*Hydroxymethyl*-4-*methoxyphenyl*)-3-*methoxyphenyl*]-2-[3-(4-*hydroxymethylphenoxy*)-4-*methoxyphenyl*]-*ethane* (**30**).—A solution of (**26**) (170 mg, 0.31 mmol) in THF (10 ml) was treated with $LiAlH_4$ (50 mg). After stirring overnight and the usual work-up, the product (**29**) was dissolved in CH_2Cl_2 and treated with CH_2N_2 in Et_2O (5 ml) [generated from *N*-nitroso-*N*-methylurea (1.0 g)]. After 5 h the solution was evaporated and the crude product purified by chromatography (eluant C_6H_6–EtOAc, 4:1) to give (**30**) (126 mg, 30%) as a resin (Found: M^+, 500. $C_{31}H_{32}O_6$ requires M^+, 500); δ(400 MHz) 2.45 (2 H, br s, OH), 2.85—2.95 (4 H, m, CH_2CH_2), 3.69, 3.81, and 3.85 (3 × 3

* The structure of (**18**) was proved by hydrolysis which gave 2-iodo-3-methoxybenzoic acid and 3-hydroxybenzaldehyde.

H, 3 × s, OMe), 4.25—4.45 (2 H, br m, 8-CH_2), 4.61 (2 H, s, 10′-CH_2), 6.69 (1 H, d, *J* 5.5 Hz, 4-H), 6.77 (1 H, d, *J* 2.0 Hz, 1′-H), 6.77 (1 H, dd, *J* 7.6 and 1.5 Hz, 2-H), 6.875 (1 H, dd, *J* 8.4 and 2.7 Hz, 11-H), 6.88 (2 H, d, *J* 8.6 Hz, 8′- and 12′-H), 6.94 (1 H, d, *J* 8.4 Hz, 4′-H), 6.98 (1 H, dd, *J* 8.4 and 2.0 Hz, 3′-H), 7.01 (1 H, d, *J* 7.6 Hz, 1-H), 7.08 (1 H, d, *J* 8.4 Hz, 12-H), 7.10 (1 H, d, *J* 2.7, 9-H), 7.26 (2 H, d, *J* 8.6 Hz, 9′- and 11′-H); *m/z* 500 (M^+, 26%), 483 (M^+ − OH, 9), 257 (11), 245 (14), 243 (100), 242 (16), 228 (29), 226 (8).

1-[4-(2-*Bromomethyl*-4-*methoxyphenyl*)-3-*methoxyphenyl*]-2-[3-(4-*bromomethylphenoxy*)-4-*methoxyphenyl*]*ethane* (**31**).—Treatment of (**30**) (126 mg, 0.25 mmol) with PBr_3, as described with (**15**), gave (**31**) in quantitative yield (Found: M^+, 628, 626, 624. $C_{31}H_{30}Br_2O_4$ requires M^+, 628, 626, 624); *m/z* 628 (21%), 626 (42), 624 (M^+, 25), 533 (11), 531 (M^+ − CH_2Br, 11), 466 (49), 451 (24), 321 (17), 319 (17), 307 (29), 305 (29), 253 (23), 239 (34), 225 (46), 211 (27), 96 (34) 94 (36), 90 (28), 82 (97), 80 (HBr, 100).

Di-O-*methylriccardin A* (**3**).—Cyclization of (**31**) (157 mg, 0.25 mmol), as described for (**5**), gave, after purification by thin layer chromatography (**3**) (35 mg, 30%) as a resin, δ(400 MHz) 2.8—3.15 (8 H, br m, 1-, 2-, 13-, and 14-H_2), 3.67 and 3.94 (2 × 3 H, 2 × s, 9- and 17-OMe), 3.88 (3 H, s, 21-OMe), 5.37 (1 H, d, *J* 2.0 Hz, 26-H), 6.24 (1 H, dd, *J* 7.6 and 1.6 Hz, 25-H), 6.44 (1 H, d, *J* 1.6 Hz, 16-H), 6.78 (1 H, dd, *J* 8.2 and 2.0 Hz, 11-H), 6.81 (1 H, dd, *J* 8.5 and 2.7 Hz, 20-H), 6.82 (1 H, d, *J* 7.6 Hz, 21-H), 6.88 (1 H, d, *J* 8.2 Hz, 10-H), 6.96 (1 H, d, *J* 2.7 Hz, 22-H), 7.05 (1 H, d, *J* 8.5 Hz, 19-H), 6.65—6.8 (4 H, br m, 4-, 5-, 27-, and 28-H); in $(CD_3)_2SO$ at 100 °C, signal for CH_2CH_2: 2.81 (4 H, s) and 2.91 (4 H, s); for 5- and 27-H: 6.76 (2 H, d, *J* 8.8 Hz); for 4- and 28-H: 6.87 (2 H, d, *J* 8.8 Hz); [lit.,[4] δ 2.61 (m), 2.84 (m), 2.92 (m), 3.09 (m), 3.65 (s), 3.86 (s), 3.92 (s), 5.36 (d), 6.23 (dd), 6.43 (d), 6.67 (br d), 6.73 (br d), 6.77 (dd), 6.82 (d), 6.87 (d), 6.88 (br d), 6.96 (d), 6.81 (dd), 7.05 (d)]; *m/z* 468 (15%), 467 (33), 466 (M^+, 100%), 240 (10), 239 (53), 233 (17), 227 (17), 225 (6) [lit.,[4] 466 (90%), 240 (20), 239 (100), 233 (14), 227 (12), 225 (15), 211 (16), 105 (11), 90 (18)].

Riccardin C (**2**).—Treatment of (**3**) (30 mg, 0.064 mmol) with boron tribromide, as described for (**4**), gave, after purification by t.l.c., (**2**) (10 mg, 37%); *m/z* 425 (22%), 424 (M^+, 69), 213 (26), 212 (28), 211 (100), 197 (10), 189 (14), 107 (13), 91 (14) [lit.,[7] 425 (24%), 424 (71), 213 (27), 212 (30), 211 (100), 197 (11), 189 (16), 149 (11), 107 (17), 91 (12)].

4-*Hydroxy*-3-(4-*methoxycarbonyl*)*benzaldehyde* (**20**).—To a solution of (**8**) (1.43 g, 5 mmol) in C_6H_6 (90 ml) was added $AlCl_3$ (3.0 g, 22 mmol) and the mixture stirred for 24 h. After treatment of the mixture with ice (50 g), the organic phase was evaporated and the residue purified by chromatography (eluant C_6H_6–butan-2-one, 20:1) to give an oil which crystallized on trituration with $CHCl_3$ (1.0 g, 73%), m.p. 136—138 °C (Found: C, 66.0; H, 4.5. $C_{15}H_{12}O_5$ requires C, 66.2; H, 4.4%); δ 3.83 (3 H, s, OMe), 6.92 (2 H, d, *J* 8.5 Hz, 2′- and 6′-H), 7.11 (1 H, d, *J* 8.5 Hz, 5-H), 7.37 (1 H, d, *J* 2.5 Hz, 2-H), 7.55 (1 H, dd, *J* 8.5 and 2.5 Hz, 6-H), 7.92 (2 H, d, *J* 8.5 Hz, 3′- and 5′-H), 9.7 (1 H, s, CHO).

4-*Benzyloxy*-3-(4-*methoxycarbonylphenoxy*)*benzaldehyde* (**21**).—(**20**) (1.36 g, 5 mmol), $PhCH_2Cl$ (0.69 g, 5.5 mmol), and K_2CO_3 (2.5 g, 18 mmol) were heated in DMF (20 ml) for 1 h at 120 °C. Dilution with water precipitated the product, which was recrystallized from MeOH (1.3 g, 60%), m.p. 107—109 °C (Found: C, 72.9; H, 4.9. $C_{22}H_{18}O_5$ requires C, 72.9; H, 5.0%); δ 3.80 (3 H, s, OMe), 5.05 (2 H, s, OCH_2), 6.7—7.4 (8 H, m, 2′-, 6′-, 5-H, and C_6H_5), 7.5—7.7 (2 H, m, 2- and 6-H), 7.90 (2 H, d, *J* 8.5 Hz, 3′- and 5′-H), 9.80 (1 H, s, CHO).

[4-*Benzyloxy*-3-(4-*methoxycarbonylphenoxy*)*benzyl*]*triphenylphosphonium Bromide* (**24**).—(**21**) (1.0 g, 2.76 (mmol) was reduced with $NaBH_4$ as described for (**9**) to give (**22**) as a low melting solid. This was transformed, without purification, to the bromide (**23**) by treatment with PBr_3 (0.81 g, 3.0 mmol) in C_6H_6 (10 ml) at room temperature for 2 h. After washing with aqueous $NaHCO_3$, the solvent was evaporated, Ph_3P (0.8 g, 3.0 mmol) in MeCN (10 ml) was added to the residue (1.17 g), and the mixture was boiled for 1 h. Evaporation and trituration of the residue with C_6H_6 gave (**24**) (1.61 g, 84%), m.p. 220—222 °C (Found: C, 69.4; H, 5.0. $C_{40}H_{34}BrO_4P$ requires C, 69.7, H, 4.9%); δ 3.90 (3 H, s, OMe), 4.96 (2 H, s, OCH_2), 5.50 (2 H, d, *J* 15 Hz, CH_2P^+), 6.6—8.0 (27 H, m, Ar-H).

(E)-*and*(Z)-1-[4-*Benzyloxy*-3-(4-*methoxycarbonylphenoxy*)]-2-[8-*Methoxy*-6-*oxodibenzo*[bd]*pyran*-3-*yl*]*ethene* (**27**).—(**19**) (290 mg, 1.14 mmol) and (**24**) (790 mg, 1.14 mmol) were reacted and worked up as described for (**25**). Layer chromatography (eluant C_6H_6–EtAOc, 8:1) gave (**27**) (0.43 g, 64%) as a resin (Found: C, 75.8; H, 4.9. $C_{37}H_{28}O_7$ requires C, 76.0; H, 4.8%); δ 3.84, 3.91, and 3.93 (3 × 3 H, 3 × s, OMe), 5.06 and 5.10 (2 × 2 H, 2 × s, OCH_2), 6.6—8.1 (20 H, m, olefinic + Ar-H).

2-[4-*Benzyloxy*-3-(4-*methoxycarbonylphenoxy*)]-1-[8-*methoxy*-6-*oxodibenzo*[bd]*pyran*-3-*yl*]*ethane* (**28**).—Hydrogenation of (**27**) (410 mg, 0.7 mmol) in EtOAc–EtOH gave (**28**) in quantitative yield, m.p. 160—162 °C (from Et_2O) (Found: M^+, 496. $C_{30}H_{24}O_7$ requires M^+, 496); δ(400 MHz) 2.86 and 2.92 (4 H, 2 × m, CH_2CH_2), 3.84 and 3.89 (2 × 3 H, 2 × s, OMe), 6.71 (1 H, d, *J* 2.0 H, 1′-H), 6.85 (2 H, d, *J* 9.0 Hz, 8′- and 12′-H), 6.92 (1 H, dd, *J* 8.2 and 2.0 Hz, 3′-H), 6.99 (d, *J* 8.2 Hz, 4′-H), 7.01 (1 H, dd, *J* 8.2 and 2.0 Hz, 2-H), 7.04 (1 H, d, *J* 2.0 Hz, 4-H), 7.34 (1 H, dd, *J* 8.9 and 2.8 Hz, 9-H), 7.73 (1 H, d, *J* 2.8 Hz, 7-H), 7.78 (1 H, d, *J* 8.2 Hz, 1-H), 7.85 (2 H, d, *J* 9.0 Hz, 9′- and 11′-H), 7.92 (1 H, d, *J* 8.9 Hz, 10-H); *m/z* 496 (M^+, 30%), 464 (31), 271 (23), 257 (100), 240 (50), 239 (75), 225 (38), 135 (69).

1-[3-*Hydroxy*-4-(2-*hydroxymethyl*-4-*methoxyphenyl*)-*phenyl*]-2-[4-*hydroxy*-3-(4-*hydroxymethylphenoxy*)*phenyl*]-*ethane* (**32**).—(**28**) (300 mg, 0.60 mmol) was reduced as described for (**14**) to give (**32**) (230 mg, 80%) as a resin (Found: C, 73.6; H, 5.8. $C_{29}H_{28}O_6$ requires C, 73.7; H, 6.0%); *m/z* 472 (M^+, 3%), 454 (67), 436 (13), 243 (10), 229 (30), 225 (100), 211 (68), 199 (29).

1-[3-*Benzyloxy*-4-(2-*hydroxymethyl*-4-*methoxyphenyl*)-*phenyl*]-2-[4-*benzyloxy*-3-(4-*hydroxymethylphenoxy*)*phenyl*]-*ethane* (**33**).—(**28**) (320 mg, 0.68 mmol), $PhCH_2Br$ (300 mg, 1.77 mmol), and K_2CO_3 (300 mg) in acetone (10 ml) were boiled with stirring for 6 h. After filtration and evaporation the residue was triturated several times with hot hexane to yield (**33**) (400 mg, 91%) as a resin (Found: C, 79.3; H, 6.1. $C_{43}H_{40}O_6$ requires C, 79.1; H, 6.2%); δ(400 MHz) 1.80 (2 H, br s, OH), 2.82—2.93 (4 H, m, CH_2CH_2), 3.86 (3 H, s, OMe), 4.3—4.4 (2 H, br m) and 4.5 (2 H, s) (CH_2OH), 4.90 and 5.06 (2 × 2 H, 2 × s, OCH_2Ph), 6.78 (1 H, d, *J* 2.0 Hz, 1′-H), 6.79 (1 H, dd, *J* 7.5 and 1.6 Hz, 2-H), 6.80 (1-H, d, *J* 1.6 Hz, 4-H), 6.88 (1 H, dd, *J* 8.5 and 2.5 Hz, 11-H), 6.89 (2 H, d, *J* 8.5 Hz, 8′- and 12′-H), 6.91 (1 H, dd, *J* 8.3 and 2.0 Hz, 3′-H), 6.95 (1 H, d, *J* 8.3 Hz, 4′-H), 7.04 (1 H, d, *J* 7.5 Hz, 1-H), 7.08 (1 H, d, *J* 2.5 Hz, 9-H), 7.09 (1 H, d, *J* 8.5 Hz, 12-H), 7.25 (2 H, d, *J* 8.5 Hz, 9′- and 11′-H), 7.1—7.3 (10 H, m, 2 × Ph).

1-[3-*Benzyloxy*-4-(2-*bromotheyl*-4-*methoxyphenyl*)*phenyl*]-2-[4-*benzyloxy*-3-(4-*bromomethylphenoxy*)*phenyl*]*ethane* (**34**).—Compound (**33**) (380 mg, 0.58 mmol) was converted, as described for (**31**), to the oily dibromide in quantitative yield (Found: C, 66.1; H, 4.8. $C_{43}H_{38}Br_2O_4$ requires C, 66.3; H,

4.9%); δ 2.83—2.93 (4 H, m, CH_2CH_2), 3.85 (3 H, s, OMe), 4.31 (2 H, br s) and 4.46 (2 H, s) (CH_2Br), 4.92 and 5.00 (2 × 2 H, 2 × s, OCH_2), 6.7—7.3 (13 H, m, Ar-H).

Riccardin A (**1**).—(**34**) (0.46 g, 0.60 mmol) in THF (20 ml) was added over 24 h to a deep purple solution obtained by stirring a small piece of sodium in THF (30 ml) containing tetraphenylethene (50 mg). After stirring for a further 24 h, the usual work-up and layer chromatography gave (**1**) (39 mg, 15%) as a colourless resin; δ (400 MHz) 2.55—3.15 (8 H, br m, CH_2CH_2), 3.90 (3 H, s, OMe), 4.4—5.2 (2 H, br s, OH), 5.35 (1 H, d, *J* 1.8 Hz, 26-H), 6.24 (1 H, dd, *J* 7.6 and 1 Hz, 25-H), 6.39 (1 H, d, *J* 1 Hz, 16-H), 6.7—6.9 (4 H, br m, 4-, 5-, 27-, and 28-H), 6.74 (1 H, dd, *J* 8.0 and 1.8 Hz, 11-H), 6.79 (1 H, d, *J* 7.6 Hz, 24-H), 6.88 (dd, *J* 8.5 and 2.5 Hz, 20-H), 6.92 (1 H, d, *J* 8.0 Hz, 10-H), 7.03 (1 H, d, *J* 2.5 Hz, 22-H), 7.10 (1 H, d, *J* 8.5 Hz, 19-H) [lit.,[4] δ 2.60 (m), 2.65 (m), 2.70 (m), 2.88 (m), 3.82 (s), 5.33 (d), 5.35 (s), 5.98 (s), 6.18 (dd), 6.36 (d), 6.69 (dd), 6.70 (br), 6.75 (d), 6.75 (br), 6.82 (dd), 6.83 (br), 6.88 (d), 6.98 (d), 7.05 (dd)].

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Paper 9/02153A
Received 23rd *May* 1989
Accepted 4th *July* 1989