Total Syntheses of the *meta,meta*-Bridged Biphenyls (±)-Myricanol and Myricanone, and of an Isomeric Biphenyl Ether, a 14-Oxa[7,1]metaparacyclophane

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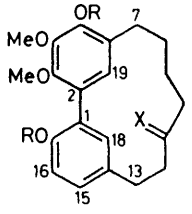
The oxidative coupling of 1,7-bis(hydroxyphenyl)heptanoids (2a,b) has been investigated: C–C coupling to *meta,meta*-bridged biaryls was not observed, but with thallium tris(trifluoroacetate) C–O coupling occurred forming a 14-oxa[7,1]metaparacyclophane analogous to the natural phenols acerogenin-A and galeon. Intramolecular reductive coupling, using tetrakis(triphenylphosphine)nickel(0), of the bis-iodides (11a,b) derived from phenols (2a,b), leads, after deprotection, to the desired *meta,meta*-bridged biphenyls myricanone and (±)-myricanol, albeit in rather low yield. *OO*-Dimethylmyricanone and (±)-*OO*-dimethylmyricanol were similarly synthesized. Irradiation (254 nm) in alkaline ethanol of the bromides (11g,h) also induced aryl–aryl coupling to form dibenzylmyricanone and (±)-dibenzylmyricanol acetate respectively.

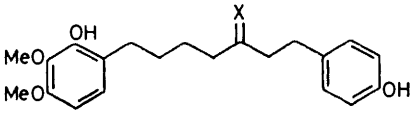
THE stem bark of the Indian tree *Myrica nagi* (Betulaceae) has various uses in folk medicine, and is piscicidal.[1] On extraction, a considerable phenolic fraction is obtained and prominent among the weakly acidic components are the structurally unusual biphenyls myricanol (1a) and myricanone (1b).[2] The former compound exhibits moderate insect-repellent activity. *X*-Ray analysis of 16-bromomyricanol showed the molecule to be strained in such a way that the biphenyl unit is not coplanar and its axis is distorted from linearity in both possible directions.[2]

In view of the theoretical interest of such structures and their potential physiological activity we undertook the total synthesis of the racemic phenols (1a) and (1b). Since the most likely biosynthesis of these biphenyls [3] involves the intramolecular oxidative coupling of a 1,7-diarylheptane such as (2a), (2b) or a close relative, we



(1)

a; R = H; X = H,OH
b; R = H, X = O=
c; R = CH_2Ph, X = O=
d; R = CH_2Ph, X = H,OAc
e; R = Me, X = O=
f; R = Me, X = H,OAc



(2)

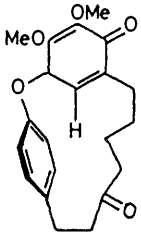
a; X = H,OH
b; X = O=
c; X = H,OAc

decided to investigate the parallel laboratory route through a one-electron oxidation of (2a) or (2b). However as the yields in such couplings are generally low, and the present case additionally involves a strained medium-sized ring it was necessary to be able to diverge the synthesis to encompass other coupling methods.

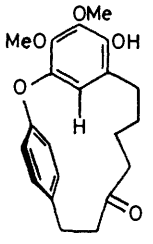
RESULTS AND DISCUSSION

In the foregoing paper [3] we described syntheses of various 1,7-diarylheptanoids including (2a—c) and various of their methyl and mono- and di-benzyl ethers. Using the alcohol (2a) a series of small-scale (10-mg substrate) oxidations were carried out, and the products analysed by t.l.c. A wide range of oxidants were employed; potassium hexacyanoferrate(III) in a two-phase system with sodium hydrogencarbonate or sodium hydroxide, aqueous iron(III) chloride, iron(III) chloride–dimethylformamide complex in ether, silver carbonate on Celite with and without added base, silver oxide–potassium carbonate or –sodium hydroxide, manganese dioxide, manganese(III) acetonylacetonate in acetonitrile, vanadium oxytrichloride, and thallium(III) tris(trifluoroacetate). In none of these reactions could myricanol (1a) [or ketone (1b)] be detected as a product. A more limited set of reactions with ketone (2b) failed to produce myricanone (1b) in any detectable quantity. In general, (2a) and (2b) were oxidised only slowly, and forcing conditions produced tars. However, in one case [treatment of (2b) with thallium tris(trifluoroacetate) [4] in dichloromethane] a relatively clean reaction ensued, from which a yellow crystalline product was obtained by p.l.c. This compound [subsequently assigned the dienone structure (3)] isomerised in solution (wet chloroform), affording a colourless solid. Mass spectrometry showed the formula to correspond to two hydrogens lost from the ketone (2b). A carbonyl (1 700 cm^{-1}) and one hydroxy (3 400 cm^{-1}, τ 4.5, exchangeable) functions were present, and the AA'BB' protons of the disubstituted aryl were intact. The methylene resonances of the 3-oxoheptane chain were present, and a single aromatic proton at relatively high field (τ 4.5). The diaryl ether structure (4) is indicated, in which, as shown by models, the two aryl rings are held with their planes approximately perpendicular by the tensed seven-membered bridge; in consequence the isolated aromatic proton is located within the shielding cone of the other aryl unit. Three natural products containing the 14-oxa[7,1]metaparacyclophane ring system displayed by (4) have very recently been described in the literature; galeon and hydroxygaleon [5] (*Myrica gale*), and acerogenin-A (5a) [6] (*Acer nikoense*). The structure of galeon rests securely on *X*-ray analysis, and that of acerogenin

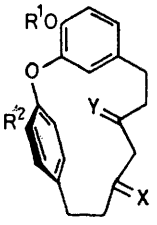
mainly on spectroscopic data relating to the derived ketone (5b): the diaryl ethers (5b) and galeon (5c) both show shielded ' inside ' aromatic protons, τ 4.47 and 4.35, respectively. Ketones (4) and (5b) show very similar n.m.r. signals for the six methylene resonances of the bridge. On electron impact (4) gave rise to fragments (*m/e* 313, 299, 285, 272, 271, and 257) formed mainly by α- and β-carbonyl and benzylic scissions while retaining the diaryl ether core. Structure (4) is thus well-founded. The oxidation may proceed by either *O*- or *C*-thalliation of the trioxygenated ring of (2b), followed



(3)



(4)



(5)

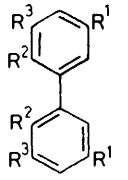
a; X = H,OH, R^1 = R^2 = Y = H
b; X = O=, R^1 = Me, R^2 = Y = H
c; Y = O=, R^1 = X = H, R^2 = OMe

by nucleophilic displacement of thallium(I) by phenolic oxygen leading initially to dienone (3). This method should be applicable to the synthesis of the natural diaryl ethers.

Since the biomimetic oxidations of (2a) and (2b) failed to produce detectable quantities of the desired *m,m*-bridged biphenyls, attention was turned to other methods of achieving the desired coupling.

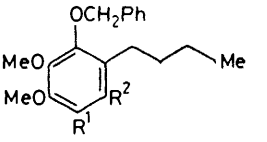
Nickel(0) reagents have been used for some years for the reductive coupling of allyl, vinyl, and aryl halides, both for symmetrical and non-symmetrical couplings. Tetracarbonylnickel(0),[7] (bis-cyclo-octadiene)nickel(0),[8] and potassium hexacyanodinickelate(0) [9] have all been employed, but recently tetrakis(triphenylphosphine)-nickel(0) [10] has been used with good results; this reagent can be generated *in situ* from the readily available bis-(triphenylphosphine)nickel(II) dichloride by zinc metal reduction.[11] Catalytic quantities [12] of the nickel reagent, with stoicheiometric amounts of zinc have been successfully used for intramolecular aryl coupling. Prompted by the report, during the progress of this work, of the use of tetrakis(triphenylphosphine)nickel(0) for intramolecular biphenyl coupling,[10] including the synthesis of the *m,m*-bridged biaryl dimethylalnusone,[13] we opted to try the same reagent.

Since the coupling has been shown [10] to be subject to steric limitations (simple reduction of the aryl halide intervening when the substrate has two *ortho*-substituents at one coupling site) we first attempted some model reactions. Thus methyl *m*-iodobenzoate, 3-iodo-4-methoxybenzaldehyde, 3-iodo-4-benzyloxybenzaldehyde, and 3-iodo-4,5-dimethoxybenzaldehyde were induced to couple to the corresponding biphenyls (6a—d) in 65, 65, 16 and 8% yields respectively. Reductive de-iodination was also observed in each case. More crowded phenyl ethers [(7a) and (8a)] were available from earlier synthetic work.[3] Iodination, using iodine–silver trifluoroacetate,[14] gave mainly the mono-iodo-product (7b) [τ 2.68 (s, 6-H) and 7.50 (t, 1′-H_2)] and in addition the bis-iodide (7c) [τ 7.08 (t, 1′-H_2)]. The deshielding effect (τ −0.42) of the *o*-iodine substituent on the benzy



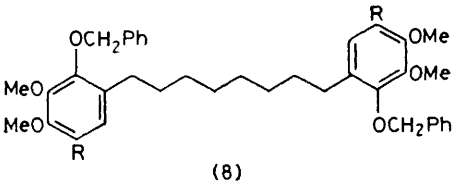
(6)

a; R^1 = CO_2Me, R^2 = R^3 = H
b; R^1 = CHO, R^2 = OMe, R^3 = H
c; R^1 = CHO, R^2 = OCH_2Ph, R^3 = H
d; R^1 = CHO, R^2 = R^3 = OMe



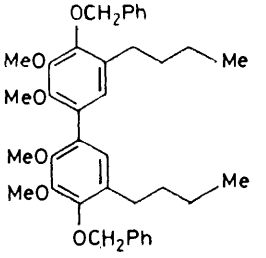
(7)

a; R^1 = R^2 = H
b; R^1 = I, R^2 = H
c; R^1 = R^2 = I



(8)

a; R = H
b; R = I



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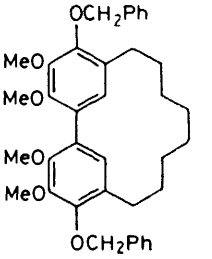
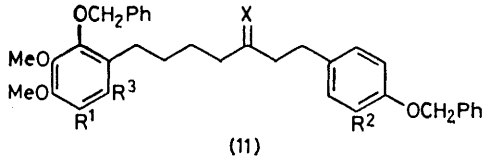


(10)

lic methylene is noteworthy. Treatment of (7b) with bis(triphenylphosphine)nickel(II) dichloride and zinc in dry dimethylformamide at 60 °C for 70 h gave the biphenyl (9), but in only 5% yield, the major product being the ether (7a). The bromide corresponding to (7b), was unchanged under the same conditions. The 1,8-

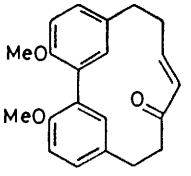
diaryloctane (8a) was bis-iodinated to (8b) (51%); exposure to the nickel(0) reagent for 118 h afforded the [8,0]metacyclophane (10) (5.5%). Comparison of the u.v. absorption of (9) and (10) shows a conjugation band in the latter spectrum (251 nm; *cf.* myricanone, 261 nm).

In the diarylheptanoid series, the dibenzyl ethers of (1a—c) were iodinated (iodine–silver trifluoroacetate) and also brominated. Substitution in the trioxygenated ring was significantly faster, so that selective halogenation, *e.g.* *OO*-dibenzyl-(2a) ⟶ (11d) could be effected. Iodination of *OO*-dibenzyl (2c) gave a little of the tri-iodoacetate (11e), *m/e* 960, as well as the di-iodoacetate

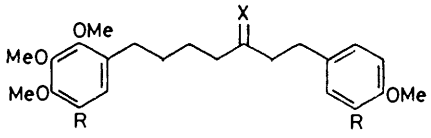


(11)

	R^1	R^2	R^3	X
a;	I	I	H	O=
b;	I	I	H	H,OAc
c;	I	I	H	H,OH
d;	I	H	H	H,OH
e;	I	I	I	H,OAc
f;	Br	Br	H	H,OAc
g;	Br	H	H	O=
h;	Br	H	H	H,OAc



(12)



(13)

a; R = H, X = O=
b; R = H, X = H,OAc
c; R = I, X = O=
d; R = I, X = H,OAc

(11b), *m/e* 834. The benzylic methylene protons (7-H_2) of (11e) resonated at τ 6.92 [*ca.* 7.40 in (11b)]. Treatment of (11a) with the nickel(0) reagent, for 72 h at 64 °C, gave dibenzylmyricanone (1c) (10%), the dibenzyl ether of (2b) (22%), and recovered starting material. Compound (1c) was identified by t.l.c., ^{1}H n.m.r., i.r., u.v., and m.s. comparison with an authentic specimen prepared from myricanone. Catalytic debenzylation then afforded myricanone, identical with a natural specimen. In a similar fashion, (11b) gave (±)-dibenzylmyricanol acetate (1d) (7%), together with the bis-deiodination product (37%), and a trace of a mono-iodide [the acetate of (11d)]. Removal of the protecting groups from (1d), in either sequence, afforded (±)-myricanol, by spectroscopic comparison with a natural sample. This completes the syntheses of the natural *m,m*-bridged biphenyls. The yields obtained at the cyclisation stage are disappointing, although net conversions can be increased by recycling. Dimethylalnusone (12) was obtained in 52% by Semmelhack and his co-workers,[10] using pre-formed tetrakis(triphenylphosphine)nickel(0) reagent. The cyclisations of (11a, b) are possibly subject to greater steric interference; moreover, study of molecular models suggests that both angle strain and van der Waals hydrogen interactions inside the macrocycle are reduced on introduction of the 4,5-double bond. The influence of chain functions on the ease of cyclisation will be the subject of further experimentation.

Two further cyclisations were performed, with the bis-iodides (13c,d) derived from the parent ethers (13a,b); incubation of (13c) for 72 h at 64 °C gave (13a) (17%) and (1e) (8%), and similar treatment of (13d) yielded (13b) and (1f) (8.5%). Yields, here and above, are of material after p.l.c.; starting materials were also recovered. The dibromide (11f) gave only some reduction product on treatment with the nickel(0) reagent.

One other method of cyclisation of the linear 1,7-diarylheptanoids was briefly examined, *viz.* the formation of biphenyls by the insertion of aryl radicals, produced by aryl halide photolysis, into phenolate anions or phenyl ethers. Such reactions have been exploited in, for example, alkaloid syntheses where photolysis of monohalogeno-isoquinolines [15] leads to Ar–Ar bond formation. The dibenzyl ether of (2a) was smoothly mono-brominated to (11g), and monobromination of the (2b) derivative gave, after acetylation, (11h). The putative products, dibenzylmyricanone and dibenzylmyricanol acetate (1d) were tested for photochemical stability by irradiating alkaline ethanol solutions with 252 nm light, in a Rayonet reactor. Although substantially degraded after *ca.* 2 h, periods of irradiation of >30 min lead only to simple debenzylation. Thus encouraged, (11g) was photolysed in ethanolic sodium hydroxide using 254-nm radiation for 30 min, after which time starting material had disappeared. Three products were isolated by p.l.c., and that of highest R_F proved to be dibenzylmyricanone (1c) (*ca.* 10% isolated material). A second product was *OO*-dibenzyl-(2b), from debromination, and a mixture of a *O*-monobenzyl-(2b) and a monobenzylmyricanone was also obtained.

The irradiation of (11h) also leads to the desired cyclisation, forming (1d), with products of concomitant debenzylation both of starting material and products. Cleavage of benzyl phenyl ether to phenol has been observed,[16] although in this case products of *o*- and *p*-*C*-benzylation were also found.

A second route to the *m,m*-bridged biphenyl system is thus feasible. Further exploration of its potential was prevented by material and time restrictions.

EXPERIMENTAL

For general information and methods, see ref. 3. Spectroscopic data are deposited as Supplementary Publication No. SUP 22659 (4 pp.).*

Thallium Tris(trifluoroacetate) Oxidation of (2b).—The title reagent (906 mg, 1.83 mmol) was suspended in dry dichloromethane (5 cm^3) and cooled to 0 °C in a dry nitrogen box. 1-(4-Hydroxyphenyl)-7-(2-hydroxy-3,4-dimethoxyphenyl)heptan-3-one (84 mg, 0.23 mmol) in dichloromethane (1 cm^3) was added to the suspension and the resulting deep red solution stirred at 0 °C for 4 h. After adding aqueous citric acid and then aqueous ammonia, the pH was adjusted to 6.0 using 2M hydrochloric acid and the aqueous part removed and extracted with dichloromethane. The organic solutions were dried and evaporated, and the residue purified by p.l.c. (chloroform–ethyl acetate, 9 : 1). The major band gave after extraction a yellow crystalline solid (3), which in chloroform solution in the presence of water slowly decolourised. Evaporation of the solution gave the *14-oxa-[7,1]metaparacyclophane* (4) (Found: *M*, 356.163. $C_{21}H_{24}O_5$ requires *M*, 356.162).

Iododiarylheptanoids and Related Compounds.—(a) (±)-*1-(4-Benzyloxyphenyl)-7-(2-benzyloxy-3,4-dimethoxy-5-iodophenyl)heptan-3-ol.* To the dibenzyl ether of (2a) (16.9 mg, 0.031 3 mmol) in dry chloroform (1 cm^3) was added, with stirring, silver trifluoroacetate (13.8 mg, 0.062 6 mmol) followed by dropwise addition over 15 min of iodine (15.9 mg, 0.062 6 mmol) in chloroform (1 cm^3). After stirring the mixture for 1 h at room temperature it was filtered and evaporated. The residue was purified by p.l.c. (n-hexane–ether, 1 : 2) to give the *title compound* (11d) (10.8 mg, 51%) as a gum (Found: *M*, 666.188. $C_{35}H_{39}IO_5$ requires *M*, 666.184), one spot on t.l.c.

(b) (±)-*1-(4-Benzyloxy-3-iodophenyl)-7-(2-benzyloxy-3,4-dimethoxy-5-iodophenyl)heptan-3-ol.* To the dibenzyl ether of (2a) (124.8 mg, 0.23 mmol) in dry dichloromethane (2 cm^3) was added silver trifluoroacetate (204 mg, 0.924 mmol) followed, during 2 h, by iodine (146.7 mg, 0.58 mmol) in dichloromethane (4 cm^3). The suspension was stirred at room temperature for 70 h. Product isolation as in (a) above gave the *title compound* (11c) (81 mg, 44%) as an oil, one spot on t.l.c. (Found: *M*, 792.088. $C_{35}H_{38}I_2O_5$ requires *M*, 792.081).

(c) *Iodination of the dibenzyl ether of* (2c). The dibenzyl ether of (2c) (124 mg) was treated as in (b), with the same molar ratio of reagents, for 17 h at room temperature, to afford, after p.l.c., *1-(4-benzyloxy-3-iodophenyl)-7-(2-benzyloxy-3,4-dimethoxy-5-iodophenyl)heptan-3-yl acetate* (11b) (72 mg, 41%), as an oil showing one t.l.c. spot (Found: *M*, 834.100. $C_{37}H_{40}I_2O_6$ requires *M*, 834.092). The same product was obtained by pyridine–acetic anhydride treatment of the alcohol (11c). At lower R_F appeared the triiodide (11e) as an oil.

(d) *1-(4-Benzyloxy-3-iodophenyl)-7-(2-benzyloxy-3,4-dimethoxy-5-iodophenyl)heptan-3-one.* The alcohol (11c) (62 mg) was treated with pyridinium chlorochromate (25 mg) in dichloromethane (2 cm^3) with stirring for 3 h. After filtration and washing, the solution was evaporated to dryness. P.l.c. of the residue gave the *title ketone* (11a) (51 mg, 82%) as an oil (one t.l.c. spot) (Found: M^+, 790.065. $C_{35}H_{36}I_2O_5$ requires *M*, 790.065).

(e) 1-(4-Methoxyphenyl)-7-(2,3,4-trimethoxyphenyl)heptan-3-ol (79 mg, 0.204 mmol) in dichloromethane (5 cm^3) was stirred with silver trifluoroacetate (90 mg, 0.408 mmol) and iodine (104 mg, 0.408 mmol) for 17 h at room temperature. Product isolation as above gave, after p.l.c., *1-(4-methoxyphenyl)-7-(2,3,4-trimethoxy-5-iodophenyl)heptan-3-ol* (11 mg) (Found: *M*, 514.118. $C_{23}H_{31}IO_3$ requires *M*, 514.122), as an oil. At lower R_F appeared 1-(3-iodo-4-methoxyphenyl)-7-(5-iodo-2,3,4-trimethoxyphenyl)heptan-3-ol (28 mg). Acetylation with pyridine–acetic anhydride at room temperature during 20 h gave the corresponding *di-iodoacetate* (13d) as an oil (one t.l.c. spot) (Found: *M*, 682.026. $C_{25}H_{34}O_6$ requires *M*, 682.029). Direct iodination (2 mol equiv. iodine reagent) over 11 h at ambient temperature of the acetate (13b) gave the di-iodoacetate (13d) in 59% yield, with, at lower R_F, 1-(3-iodo-4-methoxyphenyl)-7-(5,6-di-iodo-2,3,4-trimethoxyphenyl)heptyl-3-acetate (7%).

(f) *1-(3-Iodo-4-methoxyphenyl)-7-(5-iodo-2,3,4-trimethoxyphenyl)heptan-3-one.* The ketone (13a) (19.0 mg) was treated as in (b) above, but with stirring for 20 h. Product isolation as before gave the *title compound* (13c) as an oil (Found: *M*, 638.004. $C_{23}H_{28}I_2O_5$ requires *M*, 638.003).

(g) *1-(2-Benzyloxy-5-iodo-3,4-dimethoxyphenyl)butane.* To 1-(2-benzyloxy-3,4-dimethoxyphenyl)butane (226 mg, 0.753 mmol) in dichloromethane (10 cm^3) was added silver trifluoroacetate (250 mg, 1.13 mmol) and then, during 1 h with stirring, iodine (287 mg, 1.13 mmol) in dichloromethane (20 cm^3). After a further 24 h, the standard isolation procedure (p.l.c. with n-hexane–ether, 2 : 1) gave the *title iodide* (7b) as an oil (180 mg, 56%) (Found: *M*, 426.062. $C_{19}H_{23}IO_3$ requires *M*, 426.069). A sample of the *di-iodide* (7c) was also isolated (21%).

(h) *1,8-Bis-(2-benzyloxy-5-iodo-3,4-dimethoxyphenyl)-octane.* The 1,8-diaryloctane (8a) (49.6 mg) was iodinated as above, and the two products separated by p.l.c. From the higher R_F band was isolated the *title compound* (8b) (36 mg, 51%), m.p. 73—74.5 °C (Found: *M*, 850.123. $C_{38}H_{44}I_2O_6$ requires *M*, 850.123). The corresponding *monoiodide* was at lower R_F (8.6 mg, 14%) (Found: *M*, 724.223. $C_{38}H_{45}IO_6$ requires *M*, 724.226).

Bromodiarylheptanoids and Related Compounds.—(a) *1-(4-Hydroxyphenyl)-7-(5-bromo-2-hydroxy-3,4-dimethoxyphenyl)heptan-3-ol.* To the alcohol (2a) (29.9 mg, 0.083 mmol) in acetic acid (2 cm^3) was added during 30 min bromine (13.3 mg, 0.083 mmol) in acetic acid (1.6 cm^3). The mixture was set aside for 2 h at ambient temperature, then diluted with water and extracted with ether. Washing, drying, and evaporation of the extracts gave a residue, which was purified by p.l.c. (n-hexane–ether, 1 : 6) to yield the *title compound* (36.7 mg, 95%) as an oil (Found: *M*, 438.104. $C_{21}H_{27}BrO_5$ requires *M*, 438.104).

(b) *1-(4-Benzyloxyphenyl)-7-(2-benzyloxy-5-bromo-3,4-dimethoxyphenyl)heptan-3-ol.* The dibenzyl ether of (2a) (70 mg) was brominated as above, and the main product similarly isolated (p.l.c. with (*i*) chloroform and (*ii*) n-hexane–ether (2 : 3). It proved to be the *title alcohol* (33.6 mg, 41%), an oil (Found: *M*, 618.196. $C_{35}H_{39}BrO_5$ requires *M*, 618.198).

(c) The alcohol from (b) above (19.8 mg) was set aside for 72 h in pyridine–acetic anhydride (1 : 1). Standard isolation methods gave the *bromo-acetate* (11h) (16.8 mg, 78%) as an oil (Found: *M*, 660.213. $C_{37}H_{41}BrO_6$ requires *M*, 660.209).

* For details see Notice to Authors No. 7, *J.C.S. Perkin I*, 1978, Index issue.

(d) The alcohol from (b) above (36 mg) in dichloromethane (0.5 cm^3) was added to pyridinium chlorochromate (17.1 mg) in dichloromethane (0.5 cm^3) and the mixture stirred at room temperature for 2.5 h. After washing with water the organic solution was evaporated and purified by p.l.c. (n-hexane–ether, 2 : 3) to produce the *bromo-ketone* (11 g) (34.2 mg, 90%) as an oil (Found: *M*, 616.178. $C_{35}H_{37}BrO_5$ requires *M*, 616.182).

(e) 1-(2-*Benzyloxy*-5-*bromo*-3,4-*dimethoxyphenyl*)*butane*. Aryl ether (7a) was brominated as in (a) above, during 24 h, to yield the *title compound*, 56% after p.l.c. (Found: *M*, 378.078. $C_{19}H_{23}BrO_3$ requires *M*, 378.083). At lower R_F was obtained 1-(5-*bromo*-2-*hydroxy*-3,4-*dimethoxyphenyl*)-*butane* (20%) (Found: *M*, 288.036. $C_{12}H_{17}BrO_3$ requires *M*, 288.036).

(f) 1,8-*Bis*-(2-*benzyloxy*-5-*bromo*-3,4-*dimethoxyphenyl*)-*octane*. Diaryloctane (8a) was treated as in (e) above, to provide the *title compound* (35%), m.p. 65.5—67.5 °C (Found: *M*, 754.149. $C_{38}H_{44}Br_2O_6$ requires *M*, 754.150). The *mono-debenzylated derivative* was also detected (17%) (Found: *M*, 664.109. $C_{31}H_{38}Br_2O_6$ requires *M*, 664.104).

Biaryl Couplings using Nickel(0).—*General method*. Bis-(triphenylphosphine)nickel(II) dichloride was prepared by adding triphenylphosphine (0.04 mol) in acetic acid (50 cm^3) to nickel(II) chloride hexahydrate (0.02 mol) in water (4 cm^3) and acetic acid (100 cm^3). The greenish blue crystals were filtered off and dried *in vacuo*, m.p. 230—260 °C (decomp.) (lit.,[17] m.p. 244 °C). The salt (1 mol equiv.), triphenylphosphine (2 mol equiv.), and zinc powder (1 mol equiv.) were dried for 24 h at 0.1 mmHg over phosphorus pentaoxide, in a dry apparatus. Dry, deoxygenated, dimethylformamide (25 cm^3 per 1 mmol nickel salt) was added and the mixture stirred at 54 °C for 1 h under dry nitrogen. A red-brown slurry formed to which was added the aryl halide (1 mol equiv.) in the minimum amount of dimethylformamide. The reaction was allowed to proceed for the appropriate time, and then poured into 2% hydrochloric acid. The organic products were collected in chloroform and the chloroform solution washed, dried, and evaporated. The residues were purified by p.l.c. This method was used in the following reactions. (*a*) Methyl 3-iodobenzoate (262 mg, 1 mmol) gave (24 h, 55 °C) dimethyl biphenyl-3,3′-dicarboxylate (6a) (88 mg, 65%), m.p. 100—102 °C (lit.,[18] m.p. 104 °C) (Found: *M*, 270.089. Calc. for $C_{16}H_{14}O_4$: *M*, 270.089).

(*b*) 5-Iodo-3,4-dimethoxybenzaldehyde (292 mg, 1 mmol) gave (24 h, 56 °C) 5,5′,6,6′-tetramethoxybiphenyl-3,3′-dicarbaldehyde (6d), (13.5 mg, 8%), m.p. 212—213 °C (lit.,[19] m.p. 138—140 °C) (Found: *M*, 330.111. $C_{18}H_{18}O_6$ requires *M*, 330.110), and 3,4-dimethoxybenzaldehyde.

(*c*) 4-Benzyloxy-3-iodobenzaldehyde (338 mg, 1 mmol) gave (56 °C, 48 h) 6,6′-*bis*(*benzyloxy*)*biphenyl*-3′,3′-*dicarbaldehyde* (6c) (34 mg, 16%), m.p. 149—150 °C (from ethyl acetate–light petroleum) (Found: *M*, 422.151. $C_{28}H_{22}O_4$ requires *M*, 422.152), and 4-benzyloxybenzaldehyde.

(*d*) 3-Iodo-4-methoxybenzaldehyde (262 mg, 1 mmol) gave, at 56 °C for 24 h, 6,6′-*dimethoxybiphenyl*-3′,3′-*dicarbaldehyde* (6b) (20 mg, 16%), m.p. 131—133 °C (from light petroleum) (Found: *M*, 270.087. $C_{16}H_{14}O_4$ requires *M*, 270.089). Preparation of the reagent at 68 °C, and running the reaction at 68 °C for 22 h, raised the yield of the biphenyl to 64%.

(*e*) 4-Benzyloxy-5-n-butyl-2,3-dimethoxyphenyl iodide (7b) (150 mg, 0.353 mmol) gave, after 70 h at 60—70 °C, the reduction product 2-benzyloxy-1-n-butyl-3,4-dimethoxybenzene (28.2 mg, 27%) (by comparison with authentic material), and the 4,4′-*bis*(*benzyloxy*)-5,5′-*di*-n-*butyl*-2,2′,3,3′-*tetramethoxybiphenyl* (9) (5.4 mg, 5%), as an oil (one t.l.c. spot).

(f) 1,8-Bis-(2-benzyloxy-3,4-dimethoxyphenyl)octane (8b) (34 mg) gave, after 70 h, at 40—50 °C and 48 h at 60—70 °C 10,17-*bis*(*benzyloxy*)-11,12,15,16-*tetramethoxy*[8,0]*metacyclophane* (10) (1.3 mg. 6%).

(*g*) The bis-iodide (13c) (13.2 mg) gave after 72 h at 64 °C, *di-O-methylmyricanone* (1c) (0.6 mg, 7.5%) (Found: *M*, 384.191. $C_{23}H_{28}O_5$ requires *M*, 384.193), identified by t.l.c. (3 solvent systems), ^1H n.m.r., and m.s. comparison with an authentic sample. The reduction product (13a) (1.4 mg, 17%) was also isolated.

(*h*) The bis-iodide (13d) (9.7 mg) gave, 72 h at 64 °C (±)-*di-O-methylmyricanol acetate* (1f) (0.8 mg, 8.5%) (Found: M^+, 428.216. $C_{25}H_{32}O_6$ requires *M*, 428.219), by detailed t.l.c., m.s., and ^1H n.m.r. comparisons with authentic material.

(*i*) The bis-iodide (11a) (47 mg) yielded, after 72 h at 64 °C, *dibenzylmyricanone* (1c) (3.2 mg, 10%) (Found: *M*, 536.259. $C_{35}H_{36}O_5$ requires *M*, 536.256). T.l.c. comparison (3 solvent systems, multiple elutions) with authentic material, ^1H n.m.r., i.r., u.v., and m.s. analysis supported the identity. The product of reductive bis-deiodination was also isolated (7 mg, 22%).

(*j*) The bis-iodide (11b) (72 mg) gave, as in (*i*), the product of reductive bis-deiodination (18.4 mg, 37%) and (±)-*dibenzylmyricanol acetate* (1d) (3.7 mg, 7.3%) identified by n.m.r., u.v., m.s., and t.l.c. comparisons with a genuine specimen.

Interconversions of Derivatives of Myricanone and Myricanol.—(*a*) Dibenzylmyricanone (81 mg) in acetic acid (5.6 cm^3) was hydrogenated (Brown apparatus) over 5% palladium–carbon (100 mg), and 2 mol equiv. hydrogen were absorbed. Filtration and evaporation gave myricanone (1b) (41 mg, 75%), identical with a natural sample.

(*b*) (±)-Dibenzylmyricanol acetate (224 mg) was hydrogenated in acetic acid (10 cm^3) over 5% palladium–carbon (200 mg); 2 mol equiv. hydrogen were absorbed. Filtration and evaporation gave (±)-*myricanol acetate*, m.p. 210—212 °C (Found: *M*, 400.186. $C_{23}H_{28}O_6$ requires *M*, 400.188). Refluxing the acetate in ethanolic potassium hydroxide gave (±)-myricanol (1a), identified by t.l.c. and n.m.r. comparison with an authentic specimen.

(*c*) (−)-Myricanol (1.1 g), benzyl chloride (3 cm^3), dry potassium carbonate (15 g), and potassium iodide (2 g) in acetone (100 cm^3) were refluxed together for 20 h. After steam-distillation, the residue was ether-extracted. After washing (aqueous alkali and water), the extracts were dried and evaporated to yield (−)-*dibenzylmyricanol*, as a glass, m.p. 59—61 °C (Found: *M*, 538.274. $C_{35}H_{38}O_5$ requires *M*, 538.272). Treatment of this alcohol with pyridinium chlorochromate gave dibenzylmyricanone as a glass, m.p. 52—55 °C. Reduction of this ketone with ethanolic sodium borohydride (2 h, reflux) afforded, after product isolation through ether, (±)-dibenzylmyricanol, identical with the above specimen. Acetylation (pyridine–acetic anhydride) gave (±)-*dibenzylmyricanol acetate* [76% from (−)-myricanol], m.p. 147—148 °C (from n-hexane).

Photochemical Reactions.—(*a*) Dibenzylmyricanone (18 mg) in deoxygenated ethanol (20 cm^3) containing sodium hydroxide (4 mg) was irradiated in quartz tubes at 254 nm in a Rayonet RPR 100 reactor for 20 min. Dilution with aqueous acid and extraction into ether gave an oil (11 mg)

containing two major components. P.l.c. (chloroform) allowed separation of (*i*) starting material (2 mg), by m.s. and t.l.c. analysis, and (*ii*) one, or both, of the monobenzylmyricanones (2 mg), by mass spectrometry.

(*b*) The bromoketone (11 g) (9 mg) in deoxygenated ethanol (20 cm^3) containing sodium hydroxide (4 mg) was irradiated in quartz tubes for 30 min in a Rayonet RPR 100 reactor at 254 nm. Product isolation as above, with p.l.c. (chloroform separation) gave (*i*) dibenzylmyricanone (1 mg, 10%), by t.l.c. and m.s. comparison with an authentic sample; (*ii*) debrominated product (1 mg), by t.l.c. and m.s. comparison; and (*iii*) a mixture of a monobenzylmyricanone with a monobenzyl ether of (2b), by m.s. analysis.

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