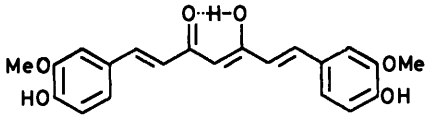
Methods for the Construction of Linear 1,7-Diarylheptanoids; Synthesis of Di-*O*-methylcentrolobol and Precursors (Synthetic and Biosynthetic) to the *meta,meta*-Bridged Biphenyls Myricanol and Myricanone

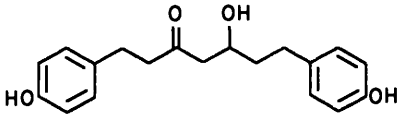
By **Peter Henley-Smith, Donald A. Whiting,* and Andrew F. Wood,** Chemistry Department, The University, Nottingham NG7 2RD

1,7-Diarylheptanoids are a varied natural product class in which ' linear ' types [*e.g.* (1), (2), and (7)] appear to be biosynthetic precursors to macro(carbo)cyclic (3), macro(oxa)cyclic (4), and condensed polycyclic (5) examples. Various methods (suitable for radiolabelling) are described for constructing ' linear ' diarylheptanoids, including Grignard couplings (employing activated magnesium) with arylpropanals and oxazonium salts [(9e), (14d), (14h) + (10), (17)→(11a), (11h), (15a), and (15b)] and dithian alkylation [(19a) + (14e)→(15c)]. Alkyllithium treatment of the benzyloxydithian (19b) gave 1,2,3-triphenylcyclopropane. Syntheses *via* trialkylcyanoborates were frustrated by disproportionation of the intermediate trialkylboranes. The diarylheptanoids synthesised (11a—h) and (15a—e) include synthetic and biosynthetic precursors to *meta,meta*-bridged biphenyls and related macrocyclic ethers.

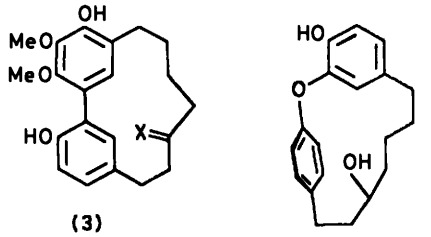
THE major orange pigment, curcumin (1), of turmeric (*Curcuma longa*) rhizome was first extracted in 1815,[1] and its structure was determined by 1910.[2] Two minor turmeric pigments were reported in 1953,[3] but no other natural products sharing the 1,7-diarylheptane carbon skeleton of curcumin were discovered until 1964; since that year over 35 compounds belonging to this emerging class of natural phenols have been described. The group includes linear diarylheptanoids found in various *Alnus* species, *A. japonica*,[4] *e.g.* platyphyllanol (2), *A. pendula*,[5] *A. hirsuta*,[6] *A. rubra*,[7] *A. firma*,[8] and in other deciduous trees, *Betula platyphylla*[6] and *Centrolobium robustum*.[9] The functional groups of the heptane chain



(1)



(2)



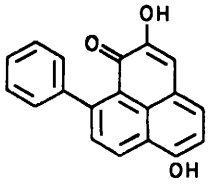
(3)
a; X = H,OH
b; X = O

(4)

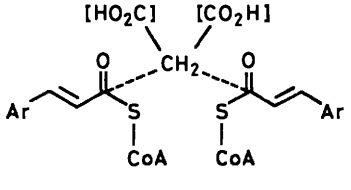
in all these compounds are formally derivable from the assembly in (1), in most cases by reduction of C=O and C=C bonds; in all cases at least one 3-oxygen function survives.

Two further sub-groups appear to be derived from linear 1,7-diarylheptanoids by oxidative phenolic coupling. Such coupling may lead *via* C–C coupling to *meta,meta*-bridged biaryls, *e.g.* myricanol (3a) and myricanone (3b) (*Myrica nagi*),[10] asadanin and its relatives (*Ostrya japonica*),[11] porson (*Myrica gale*),[12] and alnusone and relatives (*Alnus japonica*),[4] or alternatively through C–O coupling to bridged biaryl ethers, *e.g.* galeon and hydroxygaleon (*M. gale*),[13] and acerogenin-A (4) (*Acer nikoense*).[14] The co-occurrence of linear diarylheptanoids and *m,m*-bridged biphenyls in *A. japonica*, and of bridged biphenyls and biphenyl ethers in *M. gale*, lends weight to the apparent biogenetic connections; also the functionalisation of the non-aromatic carbons connects the linear and macrocyclic members of this class.

A further set of compounds derived from linear 1,7-diarylheptanoids are the 9-phenylphenalenones found in various members of the Haemodoraceae,[15–19] *e.g.* lachnanthocarpone (5).[15] This biogenetic relationship has been demonstrated by *in vivo* experiments,[20] and (5) has been synthesized from a 1,7-diarylheptanoid orthoquinone, through an intramolecular Diels–Alder sequence.[21]



(5)



(6)

The most likely biosynthesis of 1,7-diarylheptanoids involves coupling (6) of two cinnamate units to a ' central ' methylene derived from malonate, forming a molecule of the curcumin (1) type, which may then be modified as suggested above. Such an origin has been shown convincingly [20] for the phenalenones, but a direct investigation of curcumin biosynthesis [22] was not clear-cut; thus both [1-^{14}C]- and [2-^{14}C]-acetate were incorporated into curcumin in *C. longa*, with appropriate alternation of label along the heptane chain, and with

labelling of the aryl ring carbons. A second assembly route to linear diarylheptanoids is thus presumptive.

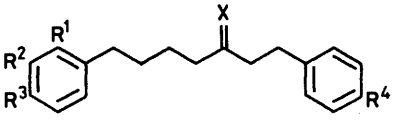
Very little synthetic work has been carried out in this area apart from the phenalenone synthesis [21] and the classic curcumin synthesis of Pabon,[23] which although valuable is limited in scope. In this paper we examine various routes to linear 1,7-diarylheptanoids, with the major objective being the synthesis of precursors whose cyclisation, both biomimetic and otherwise, to myricanol (3a) and/or myricanone (3b) could be examined. The basic requirements of a satisfactory route are (*i*) ready variation of the aryl end-groups, with either free or blocked phenolic hydroxys at both or either ends, (*ii*) the incorporation of a 3-oxygen function into the chain, and (*iii*) means for the introduction of radio-labels into the chain, for the purposes of biosynthetic experiments. The accompanying paper describes various modes of intramolecular aryl coupling of 1,7-diarylheptanoids, leading to total synthesis of (±)-myricanol, myricanone, and an analogue of acerogenin (4).

RESULTS AND DISCUSSION

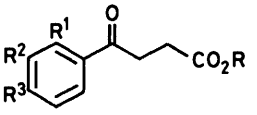
The major generalised target is thus (7), where R^1, R^2, R^3, R^4, and X are appropriate oxygen functions.

In the first, and most useful, approach to (7) an $Ar\text{-}C_4$ fragment was constructed for union with an $Ar\text{-}C_3$ unit. To this end, 1,2,3-trimethoxybenzene was reacted with succinic anhydride and aluminium chloride; acylation was accompanied by the desired *ortho*-demethylation to yield the aroylpropionic acid (8a). Yields of acid (8a) were variable, and the bis-demethylated acid (8b) was a major product; however selective methylation of (8b) to (8a) was straightforward. Hydrogenolysis of acid (8a) followed by acid-catalysed methylation provided the methyl ester (9a). Benzylation of the free hydroxy, reduction of the ester function, and conversion of the primary alcohol to bromide *via* the tosylate, *i.e.* the sequence (9a)→(9b)→(9c)→(9d)→(9e) proceeded smoothly by standard procedures. Attempted direct conversion of (9c)→(9e) with phosphorus tribromide was always accompanied by debenzylation, even in the presence of anhydrous potassium carbonate. The iodide (9f) was similarly prepared.

Efforts to generate the Grignard reagent from the bromide (9e) using standard activation methods (magnesium metal ground under inert solvent, entrainment with 1,2-dibromoethane) were fruitless. However, magnesium prepared by reduction of anhydrous magnesium chloride with potassium metal, and employed *in situ*,[24] gave reasonable yields (never optimised) of the desired Grignard reagent which was then reacted with 3-(*p*-benzyloxyphenyl)propionaldehyde (10a) (see below). The major product (42%) was the required alcohol (11a); the corresponding acetate (11b) and ketone (11c) were formed with acetic anhydride–pyridine and pyridinium chlorochromate respectively. Catalytic debenzylation of (11a) and (11c) gave the free phenols (11d) and (11e); these last two compounds are the most obvious choices (minimum modification) for the immediate biosynthetic precursors to myricanol and myricanone, although of course aryl–aryl coupling may occur in nature with the heptane chain at a different oxidation level. Partial hydrogenation of (11c) lead to preferential debenzylation in the more substituted ring, forming (11f), with a free phenolic function on the ' left-hand ' side. The alcohol (11g) of the series with a free phenolic group on the ' right-hand ' side was prepared by addition of the Grignard reagent from bromide (9e)



(7)



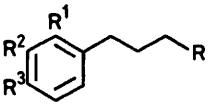
(8)

a; R = H, R^1 = OH, R^2 = R^3 = OMe

b; R = H, R^1 = R^2 = OH, R^3 = OMe

c; R = Me, R^1 = R^2 = R^3 = OMe

d; R = H, R^1 = R^2 = H, R^3 = OMe



(9)

a; R = CO_2Me, R^1 = OH, R^2 = R^3 = OMe

b; R = CO_2Me, R^1 = OCH_2Ph, R^2 = R^3 = OMe

c; R = CH_2OH, R^1 = OCH_2Ph, R^2 = R^3 = OMe

d; R = CH_2OTs, R^1 = OCH_2Ph, R^2 = R^3 = OMe

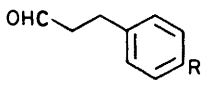
e; R = CH_2Br, R^1 = OCH_2Ph, R^2 = R^3 = OMe

f; R = CH_2I, R^1 = OCH_2Ph, R^2 = R^3 = OMe

with the methoxymethyl-protected arylaldehyde (10b); brief acid treatment removed selectively the methoxymethyl group from the product (11h). In these ways a complete range of 1,7-diarylheptanoids was produced, with an aryl oxygenation pattern corresponding to that of myricanol or myricanone, with a 3-hydroxy-, 3-acetoxy-, or 3-oxo-function as required, and with free or protected phenolic groups at either or both ends as desired. Thus halogens, or other groups which are potential radical sites, may be introduced at both or either end for studies of Ar^1–Ar^2 coupling.

In the reaction between the aldehyde (10a) with the Grignard reagent from (9e), three side-products were

isolated. One was the primary alcohol arising from reduction of (10a), presumably by an excess of active magnesium. A second product proved to be the n-butylphenol (12), produced by proton-quenching of unreacted Grignard reagent, and the remaining compound

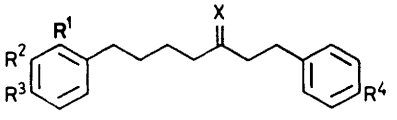


(10)

a; R = OCH_2Ph

b; R = OCH_2OCH_3

c; R = OMe



(11)

a; X = H,OH; $R^1 = R^4 = OCH_2Ph$, $R^2 = R^3 = OMe$

b; X = H,OAc; $R^1 = R^4 = OCH_2Ph$, $R^2 = R^3 = OMe$

c; X = O=; $R^1 = R^4 = OCH_2Ph$, $R^2 = R^3 = OMe$

d; X = H,OH; $R^1 = R^4 = OH$, $R^2 = R^3 = OMe$

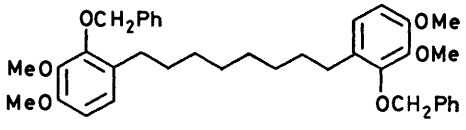
e; X = O=; $R^1 = R^4 = OH$, $R^2 = R^3 = OMe$

f; X = O=; $R^1 = OH$, $R^2 = R^3 = OMe$, $R^4 = OCH_2Ph$

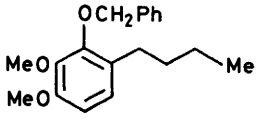
g; X = H,OH; $R^1 = OCH_2Ph$, $R^2 = R^3 = OMe$, $R^4 = OH$

h; X = H,OH; $R^1 = OCH_2Ph$, $R^2 = R^3 = OMe$, $R^4 = OCH_2OMe$

was identified as the 1,8-diaryloctane (13) formed by Grignard–bromide coupling, or a related process. Mass spectral and n.m.r. data supported these formulations, as of the other new compounds described herein; details are in the Experimental section. The products (12) and (13) found useful service in providing models for coupling reactions. Analogous compounds were observed in the



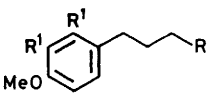
(13)



(12)

related Grignard reactions described here; formation of such side-products could probably be minimised by suitable variations for the reaction parameters, but this has not been attempted.

The aroylpropionic acids (8a) and (8b) were readily totally methylated to ester (8c). Functional manipulations parallel to those outlined above for (8a) lead through the sequence (8c)→(14a)→(14b)→(14c)→(14d); addition of the Grignard from (14d) to aldehyde (10c) provided the alcohol (15a), used in the sequel to synthesise (±)-*OO*-dimethylmyricanol and *OO*-dimethylmyricanone.



(14)

a; R = CO_2Me, R^1 = OMe

b; R = CH_2OH, R^1 = OMe

c; R = CH_2OTs, R^1 = OMe

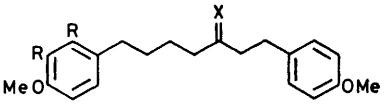
d; R = CH_2Br, R^1 = OMe

e; R = CH_2I, R^1 = OMe

f; R = CO_2Me, R^1 = H

g; R = CH_2OH, R^1 = H

h; R = CH_2Br, R^1 = H



(15)

a; X = H,OH; R = OMe

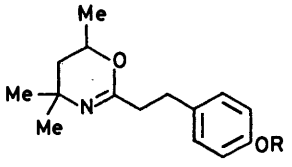
b; X = O=, R = H

c; X =  , R = OMe

d; X = O=, R = OMe

e; X = H,OH; R = H

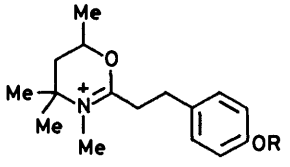
A simple variation of the basic synthetic route outlined above set out to deploy similar Grignard reagents in reaction with dihydro-oxazonium salts to form 1,7-diarylheptan-3-ones directly. 4-(*p*-Methoxyphenyl)-butyl bromide (14h) was constructed by acylation of anisole with succinic anhydride to (8d), and reduction, *etc.*, through (14f) and (14g) to (14h). 2,4,4,6-Tetramethyl-5,6-dihydro-1,3-oxazine was lithiated [25] and reacted with anisyl chloride, forming (16a). Quaternis-



(16)

a; R = Me

b; R = CH_2Ph



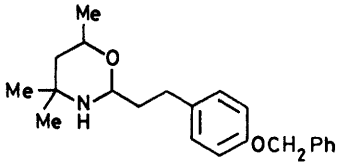
(17)

a; R = Me

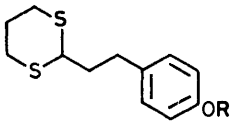
b; R = CH_2Ph

ation with methyl iodide yielded the salt (17a), which reacted smoothly with the bromo-magnesium compound from (14h) to afford 1,7-bis-(*p*-methoxyphenyl)heptan-3-one (15b). Borohydride reduction of (15b) gave (±)-*OO*-dimethylcentrolobol (15e), completing a simple synthesis of the ether of the natural phenol.[9] This route is attractive in that 3-^{14}C labelling of the diarylheptanoid could be achieved by employing 2,4,4,6-tetramethyl-5,6-dihydro-1,3-oxazine prepared from [1-^{14}C]acetic acid. However, we could not extend this route to the myricanol series since the analogous benzyl ether (17b), from methylation of (16b), failed to react with the Grignard reagent from (9e). Solubility prob-

lems may have arisen. Borohydride reduction of the dihydro-oxazine (16a) provided the perhydro-oxazine (18) which was hydrolysed to aldehyde (10a) providing a route alternative to that through the cinnamic acid.



(18)



(19)

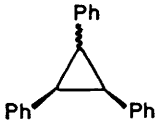
a; R = Me

b; R = CH_2Ph

c; R = H

A second variation investigated the possibilities of using bromides (9e), (14d), and (14h) as electrophilic partners in substitution with lithiated dithians prepared from arylpropanals (10a) and (10c), thus reversing the polarity of the Grignard construction reaction. Initial success was gained when dithian (19a) [prepared from the aldehyde (10c)] was lithiated with n-butyllithium and reacted, at −84 °C, with the iodide (14e); a modest yield of the required dithan (15c) was obtained, whence hydrolysis (aqueous tetrahydrofuran, mercuric chloride) yielded the corresponding ketone (15d). The last was used to prepare *OO*-dimethylmyricanone.

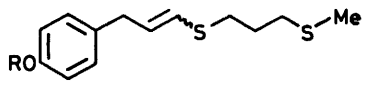
The *p*-benzyloxydithian (19b) was also treated with n-butyl-lithium, and quenched with D_2O to check carbanion formation. Apart from recovered starting material, free phenol (19c) was produced together with an equal percentage (*ca.* 10) of *cis*- and *trans*-1,2,3-triphenylcyclopropane (20) identified by comparison of



(20)

physical data with literature values: thus deprotonation at the benzylic methylene competes with abstraction of the dithian proton, and α-elimination of the phenolate anion to yield benzyl carbene rationalises the reaction. Trimerisation of pivaloyl carbene to a cyclopropane has been recorded.[26] Variation of the base type was ineffective: lithium di-isopropylamide and lithium bis-(trimethylsilylamide) did not deprotonate (19b), while sodium hydride or methyl-lithium conducted a similar reaction pathway to that with butyl-lithium. Treatment of (19b) with either of the last two bases or butyllithium followed by reaction with methyl iodide gave (19c) and (20) together with the products, (21a) and (21b), of *S*-methylation and dithian cleavage by β-elimination. Concurrent debenzylation provides (21a), and *O*-methylation then yields (21b).

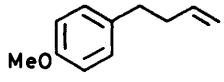
Finally an approach *via* organoboron intermediates was examined, using the general approach of Pelter.[27] Thexylborane was allowed to react at 0 °C with 4-anisylbut-1-ene (22) (from anisyl bromide and allylmagnesium bromide) and *p*-methoxystyrene (23) in various sequences, with variations in reaction times. The resulting trialkylboranes were treated with sodium



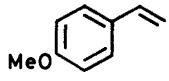
(21)

a; R = H

b; R = Me

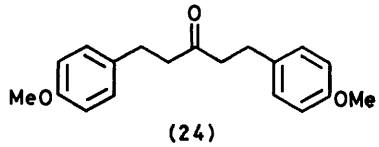


(22)

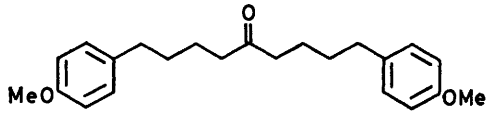


(23)

cyanide, and the resulting cyanoborates induced with trifluoroacetic anhydride to rearrange *via* 1,2 B→C alkyl shifts. Oxidation of the product gave fair yields of ketones; unfortunately the desired unsymmetrical ketone (15b) was always accompanied by the two symmetrical ketones (24) and (25). This is probably due to

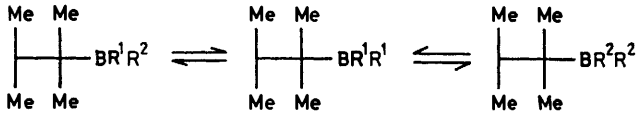


(24)



(25)

disproportionation and equilibration of the trialkylborane intermediates. With R^1 and R^2 approximately equal in steric bulk the equilibrium is not strongly biased away from any of the three boranes in equation (1) and



approximately equimolar proportions result. Since these experiments, the problem of generating, and holding, specific mixed trialkylborane structures $BR^1R^2R^3$ has been recognized [28] in the literature.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage apparatus. Thin-layer chromatography used Woelm silica TSC containing 0.5% fluorescing agent (254 nm): for preparative work, 20 × 20 or 45 × 45 cm plates coated at

0.8 mm were employed, and eluted with ethanol before use. Dry-column chromatography used Kieselgel 254 (Fluka AG); wet columns were packed with silica MFC (Hopkins and Williams). In n.m.r. measurements, tetramethylsilane was used as internal standard; s = singlet, d = doublet, t = triplet, m = multiplet. U.v. data were collected from ethanol solutions. Accurate mass measurements were made with an A.E.I. MS902 spectrometer. Most of the spectroscopic data are collected in a Supplementary Publication No. SUP 22658 (10 pp.).*

1,2,3-*Trimethoxybenzene*.—Sodium hydroxide (196 g) in water (400 cm³) was added dropwise over 2.5 h to a mixture, stirred at 0 °C under natural gas, of pyrogallol (100 g), sodium dithionite (10 g), and dimethyl sulphate (400 cm³) in methanol (200 cm³) and water (50 cm³). After 5 h at 0 °C, water (200 cm³) was added and the mixture set aside for 16 h. The product was recovered by filtration, treated with aqueous ammonia to destroy excess of methyl sulphate, washed, dried, and recrystallised from aqueous ethanol or light petroleum to yield the title compound (124 g, 93%), m.p. 43.5—44 °C (lit.,[29] m.p. 47 °C); *m/e* 168 (M^+, 100%).

3-*Aroylpropionic Acids*.—(*a*) To a stirred suspension of 1,2,3-trimethoxybenzene (42 g) and succinic anhydride (24 g) in 1,1,2,2-tetrachloroethane (160 cm³) at 0 °C, was added aluminium chloride (75 g) at such a rate as to maintain a reaction temperature of 0 °C. The red mixture was allowed to warm to ambient temperature, and after 16 h it was heated on a steam-bath for 2 h. The product was stirred with hydrochloric acid–water (1 : 1) and steam-distilled. The residue separated into an organic and an aqueous phase. The organic phase was collected and dissolved in methanol (80 cm³) with dimethyl sulphate (25 cm³), sodium dithionite (5 g, in the minimum of water) and sodium hydroxide (20 g, in the minimum of water). The solution was set aside for 21 h and then refluxed for 24 h with additional alkali for saponification. Acidification of the cooled mixture, and crystallisation of the precipitate from benzene or water gave 3-(2-hydroxy-3,4-dimethoxybenzoyl)propionic acid (8a), m.p. 154—156 °C (lit.,[30] m.p. 152 °C), in variable (30—40%) yield. Refluxing with methanol–1% sulphuric acid gave the corresponding *methyl ester*, m.p. 99—101 °C.

Collection of the organic phase before methylation, and recrystallisation from benzene and then water, gave 3-(2,3-*dihydroxy*-4-*methoxybenzoyl*)*propionic acid* (8b), m.p. 174—176 °C. The residual aqueous phase obtained after steam-distillation was extracted with ether to yield a sample of 3-(2,3,4-*trihydroxybenzoyl*)*propionic acid*.

Repetition of the reaction, but using an excess of dimethyl sulphate (and additional alkali as necessary), heating (on steam) at the methylation stage, and omitting the subsequent saponification gave *methyl* 3-(2,3,4-*trimethoxybenzoyl*)*propionate* (8c), m.p. 41—42 °C [from light petroleum (60—80 °C)] (Found: C, 59.4; H, 6.75%; *M*, 282.110. $C_{14}H_{18}O_6$ requires C, 59.55; H, 6.4%; *M*, 282.110).

(*b*) Aluminium chloride (50 g) was added in one portion to a vigorously stirred mixture of anisole (40 g) and succinic anhydride (17 g) in benzene (50 cm³); an exothermic reaction followed. The mixture was then kept at 60 °C for 0.5 h. With cooling and stirring water (80 cm³) and then concentrated hydrochloric acid (25 cm³) was added, and the mixture was steam-distilled. The residual solid was collected, washed (dilute hydrochloric acid, water), and extracted with aqueous sodium carbonate. The alkaline solution was decolourised (charcoal), and acidified. The acid product was filtered off, and recrystallised from ethanol yielding 3-(4-methoxybenzoyl)propionic acid, (8d) (27 g, 77%), m.p. 148—151 °C (lit.,[31] m.p. 147—148 °C).

4-*Arylbutanoic Acids and Esters*.—(*a*) (*i*) 3-(2-Hydroxy-3,4-dimethoxybenzoyl)propionic acid (5 g) in acetic acid (110 cm³) was hydrogenated at 64 °C over 10% palladium–carbon (500 mg): 2 mol equiv. of hydrogen was absorbed during 4 h. Isolation of the product through evaporation and dilution with water gave 4-(2-hydroxy-3,4-dimethoxyphenyl)butanoic acid (3.7 g, 77%), m.p. 96—98 °C (lit.,[30] m.p. 103 °C). Esterification with methanol–0.5% sulphuric acid gave the *methyl ester* (9a), m.p. 56.5—58 °C (Found: C, 61.4; H, 7.15. $C_{13}H_{18}O_5$ requires C, 61.4; H, 7.15%).

(*ii*) Methyl 3-(2-hydroxy-3,4-dimethoxybenzoyl)propionate (13.53 g) in acetic acid (250 cm³) was hydrogenated over 10% palladium–carbon (2.5 g) at ambient temperature and pressure until uptake of gas ceased. Filtration, evaporation of the solvent, collection of the product in ether, and washing, *etc.*, gave the above ester (9a) (12.2 g, 96%), m.p. 56.5—58 °C.

(*iii*) 3-(2-Hydroxy-3,4-dimethoxybenzoyl)propionic acid (2 g), zinc amalgamate [from zinc (3 g) and mercuric chloride (3 g)] and concentrated hydrochloric acid (7.5 cm³) were refluxed together for 3 h. The mixture was set aside overnight and the above acid (0.8 g, 41%) crystallised. From the mother-liquors were obtained 4-(2,3-dihydroxy-4-methoxyphenyl)butanoic acid, m.p. 124—125 °C.

(*b*) Methyl 3-(2,3,4-trimethoxybenzoyl)propionate (24 g) in acetic acid (300 cm³) was hydrogenated, at ambient pressure and temperature, over palladium–carbon (2.5 g); 2 mol equiv. hydrogen were absorbed in 1.5 h. Work-up as before gave *methyl* 4-(2,3,4-*trimethoxyphenyl*)*butanoate* (14a) (20 g, 88%), b.p. 186—188° (8 mmHg), $n_D^{23.5}$ 1.505 5 (Found: *M*, 268.129. $C_{14}H_{20}O_5$ requires *M*, 268.131).

(*c*) Powdered zinc (120 g) was amalgamated with mercuric chloride (12 g) in dilute hydrochloric acid, and to it were added in sequence, water (75 cm³), concentrated hydrochloric acid (175 cm³), toluene (100 cm³), and 3-(4-methoxybenzoyl)propionic acid (50 g). The mixture was refluxed for 24 h: two 60-cm³ portions of hydrochloric acid were added during the reflux. The organic phase was steam-distilled in the presence of 2M sodium hydroxide, and the residue methylated with dimethyl sulphate (50 cm³) at reflux for 1 h. On acidification 4-(4-methoxyphenyl)-butanoic acid was obtained (38.5 g, 83%), m.p. 59—61 °C (lit.,[31] m.p. 59—60 °C).

(*d*) Methyl 4-(2-hydroxy-3,4-dimethoxyphenyl)butanoate (10 g), benzyl chloride (8 cm³), and acetone (100 cm³) were refluxed over anhydrous potassium carbonate (14 g) for 48 h. The organic solution was evaporated and diluted with ether. The ether phase was washed (aqueous alkali and water), dried, and evaporated; the residual oil was purified by dry column chromatography, eluting with chloroform, to yield *methyl* 4-(2-*benzyloxy*-3,4-*dimethoxyphenyl*)*butanoate* (9b) (12.3 g, 91%), single spot on t.l.c. (n-hexane–ether, 1 : 2) (Found: *M*, 344.164. $C_{20}H_{24}O_5$ requires *M*, 344.162).

4-*Arylbutanols*.—(*a*) To lithium aluminium hydride (3.3 g) in dry ether (100 cm³) was added methyl 4-(2-benzyloxy-3,4-dimethoxyphenyl)butanoate (15 g) in ether (80 cm³) during 1 h, with stirring, and the suspension refluxed for 2 h. Cooling and standard aqueous product isolation gave 4-(2-*benzyloxy*-3,4-*dimethoxyphenyl*)*butan*-1-*ol* (9c) (14 g, 100%),

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

b.p. 188 °C (0.1 mmHg), $n_D^{23.0}$ 1.549 9, single spot on t.l.c. (n-hexane–ether, 1 : 2) (Found: *M*, 316.166. $C_{19}H_{24}O_2$ requires *M*, 316.167).

(*b*) Similar treatment of methyl 4-(2,3,4-trimethylphenyl)butanoate (10 g) gave the corresponding 4-(2,3,4-*trimethoxyphenyl*)*butanol* (14b) (5.3 g, 59%), $n_D^{21.0}$ 1.518 2, after purification by dry-column chromatography to one spot on t.l.c. (Found: *M*, 240.136. $C_{13}H_{20}O_4$ requires *M*, 240.136).

(*c*) 4-(4-Methoxyphenyl)butanoic acid (16 g) was reduced in the same manner to give 4-(4-methoxyphenyl)butanol (14 g) (100%), b.p. 180 °C (20 mmHg) [lit.,[32] b.p. 160—161° (8 mmHg)].

4-*Aryl*-1-*halogenobutanes*.—(*a*) To 4-(2-benzyloxy-3,4-dimethoxyphenyl)butanol (5.75 g) in dry pyridine (60 cm^3) at 0 °C was added, with stirring, *p*-toluenesulphonyl chloride (6.97 g). Stirring at 0 °C was continued for 3 h and the mixture kept at −5 °C for 24 h. After dilution with water the product was collected in ether; washing, *etc.* gave an oil purified to single spot on t.l.c by dry-column chromatography (n-hexane–ether, 1 : 2) to yield the *p*-toluenesulphonate (9d) (7.35 g, 88%) as an oil, $n_D^{23.0}$ 1.561 0; recrystallisation at −78 °C from light petroleum (b.p. 40—60 °C) was possible (Found: *M*, 470.175. $C_{26}H_{30}O_6S$ requires *M*, 470.176). Treatment of this *p*-toluenesulphonate (6.74 g) with lithium bromide (3.75 g) in acetone (50 cm_3) at ambient temperature for 24 h gave 4-(2-*benzyloxy*-3,4-*dimethoxyphenyl*)-1-*bromobutane* (9e) (4.75 g, 89%), $n_D^{23.5}$ 1.561 5, purified by dry-column chromatography (chloroform elution) to show one t.l.c. spot (Found: *M*, 378.081. $C_{19}H_{23}BrO_3$ requires *M*, 378.083).

(*b*) 4-(2,3,4-Trimethoxyphenyl)butanol (2.55 g) was similarly converted, with pyridine–*p*-toluenesulphonyl chloride, to the corresponding *tosylate* (14c) (2.62 g, 62%), $n_D^{23.5}$ 1.541 0 (Found: *M*, 394.145. $C_{20}H_{26}O_6S$ requires *M*, 394.145). Reaction with lithium bromide in acetone, as above, afforded 4-(2,3,4-*trimethoxyphenyl*)-1-*bromobutane* (14d) (1.60 g, 80%), $n_D^{23.5}$ 1.530 5, purified to show one spot on t.l.c. by dry-column chromatography (chloroform) (Found: *M*, 302.053. $C_{13}H_{19}BrO_3$ requires *M*, 302.052). In a similar way, using lithium iodide–acetone over 16 h at room temperature, was prepared 4-(2,3,4-*trimethoxyphenyl*)-1-*iodobutane* (14c) (88%), $n_D^{24.0}$ 1.554 3.

(*c*) 4-(4-Methoxyphenyl)butanol (4 g was treated at 0 °C and with stirring with phosphorus tribromide (2 g) over 2 h. The temperature was allowed to rise to ambient and after 4 h the mixture was poured into water. Extraction into ether and washing, drying, and evaporation of the ethereal extracts gave 4-(4-methoxyphenyl)-1-bromobutane (14h) (2.0 g, 37%), b.p. 114 °C (0.02 mmHg).

4,4,6-*Trimethyl*-2-(2-*arylethyl*)-5,6-*dihydro*-4H-1,3-*oxazines*.—(*a*) 2,4,4,6-Tetramethyl-5,6-dihydro-1,3-oxazine (2.8 g, 0.02 mol) in dry tetrahydrofuran (20 cm^3) was cooled to −78 °C and n-butyl-lithium (0.02 mol, hexane solution) was added over 0.75 h. After 1 h formation of a yellow precipitate was complete and anisyl chloride (3.4 g, 0.022 mol) in tetrahydrofuran (2 cm^3) was added over 0.5 h. The reaction temperature was then allowed to rise to ambient; the solution was mixed with water (20 cm^3), acidified to pH 2—3 and washed with n-pentane. On basification, at 0 °C, of the aqueous part a yellow oil was obtained, yielding on distillation 4,4,6-*trimethyl*-2-(2-p-*methoxyphenylethyl*)-5,6-*dihydro*-4H-1,3-*oxazine* (16a) (4.4 g, 86%), b.p. 130—131 °C (1.2 mmHg) (Found: C, 73.4; H, 8.95; N, 5.05. $C_{16}H_{32}NO_2$ requires C, 73.55; H, 8.85; N, 5.35%).

(*b*) In a similar manner, 4-benzyloxybenzyl chloride[33] (3.2 g, 0.014 mol) was converted to 2-(2-p-*benzyloxyphenylethyl*)-4,4,6-*trimethyl*-5,6-*dihydro*-1,3-*oxazine* (16b) (4.4 g, 88%), b.p. 185—186° (0.3 mmHg) (Found: C, 77.7; H, 8.15; N, 4.0. $C_{22}H_{27}NO_2$ requires C, 78.30; H, 8.05; N, 4.15%). On standing in air hydrolytic cleavage of the heterocycle occurred, yielding N-(1,1-*dimethyl*-3-*hydroxybutyl*)-3-(4-*benzyloxyphenyl*)*propionamide*, m.p. 73—75 °C (from n-hexane) (Found: C, 73.7; H, 8.65; N, 4.05. $C_{22}H_{29}NO_3$ requires C, 74.2; H, 8.15; N, 3.95%).

3-*Arylpropanals*.—(*a*) (*i*) To lithium aluminium hydride (4 g) in dry ether (100 cm^3) was added, during 0.5 h, 3-(4-benzyloxyphenyl)propionic acid[34] (10 g) in ether (300 cm^3). The mixture was refluxed under nitrogen, with stirring, for 2.5 h. The product was isolated in the usual way; recrystallisation from aqueous ethanol gave 3-(4-*benzyloxyphenyl*)*propan*-1-*ol* (10a) (8.16 g, 85%), m.p. 64.5—65.5 °C (Found: C, 79.4; H, 8.05%; *M*, 242.133. $C_{16}H_{18}O_2$ requires C, 79.35; H, 7.45%; *M*, 242.131). The alcohol (5.21 g) in dichloromethane (40 cm^3) was added with stirring, at room temperature, to pyridinium chlorochromate (6.93 g) in dichloromethane (40 cm^3). After 24 h the mixture was diluted with ether and filtered through a short Florisil column; the colourless filtrate was evaporated to give 3-(4-*benzyloxyphenyl*)*propanal* (10a) (4.02 g, 78%), m.p. 59—61 °C (Found: *M*, 240.115. $C_{16}H_{16}O_2$ requires *M*, 240.115). A bisulphite addition compound, m.p. 140—142 °C, could be formed, and also a 2,4-dinitrophenylhydrazone, m.p. 152—154 °C.

(*ii*) The above (2-*p*-benzyloxyphenylethyl)dihydro-oxazine (32 g) in tetrahydrofuran (112 cm^3), ethanol (128 cm^3), and water (8 cm^3) was cooled to −40 °C, and sodium borohydride (5 g) in water (12 cm^3) was added during 0.75 h. The pH was maintained below 8 by addition of hydrochloric acid. After a further 1 h, the mixture was diluted with water, basified, and ether-extracted. The usual product recovery gave 2-(2-*p*-benzyloxyphenylethyl)-4,4,6-trimethylperhydro-1,3-oxazine (18) (26.2 g, 77%), b.p. 203—210 °C (14 mmHg). This intermediate (1 g) was hydrolysed by refluxing in water (5 cm^3) with oxalic acid hydrate (1.5 g) for 4.5 h. Ether extraction, *etc.*, gave the above aldehyde (0.45 g, 63.5%).

(*b*) 3-(4-Methoxyphenyl)propan-1-ol[35] (4.41 g) (from reduction of the corresponding acid) in dichloromethane (40 cm^3) was added to pyridinium chlorochromate (8.7 g) in dichloromethane (40 cm^3), and the mixture stirred for 4.5 h. After dilution with dry ether, the solution was filtered through Florisil and evaporated. Dry column chromatography (chloroform) gave 3-(4-*methoxyphenyl*)*propanal* (10c) (3.3 g, 74%), n_D^{24} 1.523 7, one spot on t.l.c. (Found: *M*, 164.081 $C_{10}H_{12}O_2$ requires *M*, 164.084). It formed a 2,4-dinitrophenylhydrazone, m.p. 138—141 °C.

(*c*) 3-(4-Benzyloxyphenyl)propan-1-ol (6.08 g) in glacial acetic acid (100 cm^3) was hydrogenated over 10% palladium–carbon (1 g). Filtration, evaporation, and dilution with water gave the product, collected in ether. Washing, *etc.*, of the ethereal solution gave 3-(4-hydroxyphenyl)propan-1-ol (3.4 g, 89%), m.p. 48.5—51.5 °C (lit.,[36] m.p. 55 °C) (Found: *M*, 152.082. Calc. for $C_9H_{12}O_2$, *M*, 152.084). To a stirred, refluxing, mixture of this phenol (7.6 g) and anhydrous potassium carbonate (30 g) in acetone (200 cm^3) was added dropwise chloromethyl methyl ether (10 g) in acetone (30 cm^3), over 0.25 h. After a further 0.5 h, water was added, and excess of reagent destroyed by refluxing. After evaporation of solvent, the product was extracted

into ether; washing, *etc.*, gave 3-(4-*methoxymethoxyphenyl*)-*propan*-1-*ol* (4.08 g), purified to one spot on t.l.c. by dry-column chromatography (n-hexane–ether, 1 : 5) (Found: *M*, 196.110. $C_{11}H_{16}O_3$ requires *M*, 196.109). Some starting material was recovered. Finally, oxidation with pyridinium chlorochromate as described above afforded 3-(4-*methoxymethoxyphenyl*)*propanal* (10b) (51%), $n_D^{25.0}$ 1.513 (Found: *M*, 194.095. $C_{11}H_{14}O_3$ requires *M*, 194.094); it gave a 2,4-dinitrophenylhydrazone, m.p. 125—128 °C.

Grignard Reactions.—(*a*) A mixture of anhydrous magnesium chloride (0.701 g, 7.38 mmol), potassium metal (0.52 g, 13.24 mmol), and potassium iodide (0.55 g, 3.31 mmol) in dry tetrahydrofuran (25 cm³) were refluxed for 2 h under nitrogen. The resulting black slurry was cooled to room temperature and 4-(2-benzyloxy-3,4-dimethoxyphenyl)-1-bromobutane (1.1 g, 2.92 mmol) was added in one portion (slow addition of the bromide improved the yield substantially, see below). After 0.5 h, 3-(4-benzyloxy phenyl)propanal (0.698 g, 2.91 mmol) was added, and the reaction mixture stirred at room temperature for 18 h. The resulting slurry was cautiously quenched with water, under nitrogen; dilute aqueous acid was added, and the organic products extracted into ether. Washing, *etc.*, of the extracts gave an oil which was resolved by p.l.c. (n-hexane–ether, 1 : 3). Four major products were purified (to one t.l.c. spot) and identified; in decreasing order of R_F these were (*i*) 1-(2-*benzyloxy*-3,4-*dimethoxyphenyl*)*butane* (12) as an oil (Found: *M*, 300.172. $C_{19}H_{24}O_3$ requires *M*, 300.172); (*ii*) 1,8-*bis*-(2-*benzyloxy*-3,4-*dimethoxyphenyl*)*octane* (13) as an oil (Found: *M*, 598.332. $C_{38}H_{46}O_6$ requires *M*, 598.329); (*iii*) 3-(4-benzyloxyphenyl)propan-1-ol, identified by comparison (t.l.c., n.m.r.) with an authentic sample; and (*iv*) the desired product, (±)-1-(4-benzyloxyphenyl)-7-(2-benzyloxy-3,4-dimethoxyphenyl)heptan-3-ol (11a), as an oil (0.28 g, 17.8%); modification by dropwise addition of the bromide to magnesium over 2 h increased the yield to 42%; otherwise the yield was not optimised) (Found: *M*, 540.288. $C_{35}H_{40}O_5$ requires *M*, 540.287). The corresponding *acetate* (11b) was formed (73%) using pyridine–acetic anhydride, and purified by p.l.c. (n-hexane-ether, 1 : 1) (Found: *M*, 582.302. $C_{37}H_{42}O_6$ requires *M*, 582.298). Oxidation of the alcohol with pyridinium chlorochromate in dichloromethane provided (75%) the corresponding *ketone* (11c) as a gum, purified by p.l.c. (n-hexane–ether, 2 : 3) (Found: *M*, 538.272. $C_{35}H_{38}O_5$ requires *M*, 538.272).

(*b*) A magnesium suspension was prepared from anhydrous magnesium chloride (0.91 g, 9.6 mmol), potassium iodide (0.72 g, 4.3 mmol), and potassium metal (0.67 g, 17.22 mmol), refluxed together for 2 h under nitrogen in dry tetrahydrofuran (30 cm³). To the cooled product was added 4-(2,3,4-trimethoxyphenyl)-1-bromobutane (1.28 g, 4.2 mmol) and after initial warming the mixture was stirred for 1 h. 3-(4-Methoxyphenyl)propanal (0.69 g, 4.2 mmol) was added and the mixture stirred overnight. After quenching with saturated aqueous ammonium chloride (under nitrogen, with care) the organic products were extracted into ether and separated as in (*a*) above. Four main components were isolated and repurified by p.l.c. until showing one spot on t.l.c. analysis: they were in order of decreasing R_F; (*i*) 1-(2,3,4-*trimethoxyphenyl*)-*butane*, (16%), $n_D^{23.5}$ 1.4984 (Found: *M*, 224.139. $C_{13}H_{20}O_3$ requires *M*, 224.141); (*ii*) 1,8-*bis*(*trimethoxyphenyl*)-*octane* (10%), $n_D^{23.5}$ 1.526 1 (Found: *M*, 446.266. $C_{26}H_{38}O_6$ requires *M*, 446.267); (*iii*) (±)-1-(4-*methoxyphenyl*)-7-(2,3,4-*trimethoxyphenyl*)*heptan*-3-*ol* (15a) (253 mg, 16%, not optimised, see above) (Found: *M*, 388.221. $C_{23}H_{32}O_5$ requires *M*, 388.225). Acetic anhydride-pyridine gave the corresponding *acetate* (72) (Found: *M*, 430.233. $C_{25}H_{34}O_6$ requires *M*, 430.235), and pyridinium chlorochromate in dichloromethane afforded the corresponding *ketone* (15d) (75%) (Found: *M*, 386.204. $C_{23}H_{30}O_5$ requires *M*, 386.209). Both compounds were gums, purified by p.l.c. to show a single t.l.c. spot. Finally, (*iv*), 3-(4-methoxyphenyl)-propan-1-ol was identified by t.l.c. and n.m.r. comparison with an authentic specimen.

(*c*) Active magnesium was prepared as above [magnesium chloride (0.821 g), potassium iodide (0.64 g), potassium metal (0.605 g), and tetrahydrofuran (25 cm³)] and 4-(2-benzyloxy-3,4-dimethoxyphenyl)-1-bromobutane (1.4 g) added during 5 min. After 30 min, 3-(4-methoxymethoxyphenyl)-propanal (0.75 g) was added and the reaction mixture stirred overnight. Product isolation as above gave a mixture with three main components: separation by p.l.c. (n-hexane–ether, 1 : 1) gave, at lowest R_F, (±)-1-(4-*methoxymethoxyphenyl*)-7-(2-*benzyloxy*-3,4-*dimethoxyphenyl*)-*heptan*-3-*ol* (11h) (0.4 g, 21%, not optimised, see above) (Found: *M*, 494.269. $C_{30}H_{38}O_6$ requires *M*, 494.267).

(*d*) 4,4,6-Trimethyl-2-(2-*p*-methoxyphenylethyl)-5,6-dihydro-4*H*-1,3-oxazine (0.197 g, 0.7 mmol) and dry methyl iodide (1 cm³) were stirred overnight, and the resulting salt washed with ether by decantation and dried *in vacuo*. 1-Bromo-4-(4-methoxyphenyl)butane (1 g) was reacted with magnesium metal (0.2 g) in dry ether, and the resulting Grignard reagent added to the oxazonium salt; the mixture was stirred for 18 h, decomposed with ice–water, and extracted with ether. The ethereal extracts were evaporated and the residual 2,2-dialkyloxazine hydrolysed with oxalic acid (1.2 g) and water (10 cm³) at reflux for 1 h. Ethereal extracts of the product were washed, dried, and evaporated. The residue was purified by p.l.c. to yield 1,7-*bis*-(4-*methoxyphenyl*)*heptan*-3-*one* (15b) (46 mg, 19%), one peak on g.l.c. (see below) (Found: *M*, 326.188. $C_{21}H_{26}O_3$ requires *M*, 326.188). The ketone (27 mg), ethanol (11 cm³), and sodium borohydride (68 mg) were stirred at room temperature for 20 h. After evaporation, water was added and the mixture was ether extracted. The residue from the extracts after drying and evaporation was purified by p.l.c. (chloroform) to yield (±)-*di*-*O*-*methylcentrolobol* (15c), m.p. 37.5—38.5 °C (from light petroleum) (14 mg, 50%) (Found: *M*, 328.205. $C_{21}H_{28}O_3$ requires *M*, 328.204).

2-(2-*Arylethyl*)-1,3-*dithians.*—(*a*) To dihydrocinnamaldehyde (8.6 g) and propane-1,3-dithiol (6.9 g) in acetic acid (10 cm³) was added with stirring boron trifluoride etherate (22.7 g) in acetic acid (10 cm³). After 3 h at room temperature the mixture was diluted with water, neutralised (aqueous sodium hydroxide), and extracted with chloroform. The extracts were washed, dried, and evaporated and the residue distilled to provide 2-(2-phenylethyl)-1,3-dithian (19c) (14.05 g, 97%), b.p. 62—65 °C (0.25 mmHg) [lit.,[37] b.p. 130 °C (6 mmHg)].

(*b*) 3-(4-Benzyloxyphenyl)propanal (2 g) and propane-1,3-dithiol (0.9 g) were stirred together in dichloromethane (25 cm³) for 1 h. The mixture was cooled to −25 °C and hydrogen chloride bubbled through for 0.5 h. The solution was allowed to warm to room temperature during 1.5 h, and then washed, dried, and evaporated. Separation of the residual oil by dry-column chromatography gave 2-(2-*p*-*benzyloxyphenylethyl*)-1,3-*dithian* (19b) (1.32 g, 48%), m.p. 59—62 °C (from n-hexane) (Found: C, 69.1; H, 6.9; S,

18.35%; *M*, 330.113. $C_{19}H_{22}OS_2$ requires C, 69.1; H, 6.65; S, 19.4%; *M*, 330.111).

(*c*) 3-(*p*-Methoxyphenyl)-1,3-dithian (1.1 g), propane-1,3-dithiol (0.72 g), and dichloromethane (30 cm^3) were stirred together for 1 h and the mixture cooled to −25 °C. Hydrogen chloride was passed in for 0.5 h, and the solution set aside for 1.5 h, at ambient temperature. Product isolation as in (*b*) gave 2-(2-p-*methoxyphenylethyl*)-1,3-*dithian* (19a) (0.75 g, 54%), m.p. 47—48 °C from n-hexane (Found: C, 61.25; H, 7.0%; *M*, 254.081. $C_{13}H_{18}OS_2$ requires C, 61.4; H, 7.05%; *M*, 254.079).

Preparation of 1-(4-*Methoxyphenyl*)-7-(2,3,4-*trimethoxyphenyl*)*heptan*-3-*one by Dithian Alkylation.*—To 2-(2-*p*-methoxyphenylethyl)-1,3-dithian (0.127 g, 0.5 mmol) in dry tetrahydrofuran (1 cm^3) at −35 °C was added, over 5 min, n-butyl-lithium (0.55 mmol, 2M solution). The solution was stirred for 3 h, and became pale yellow; it was cooled to −84 °C, and 4-(2,3,4-trimethoxyphenyl)-1-iodobutane (0.175 g, 0.5 mmol) was added. After 4 h at −84 °C (a white precipitate had appeared) the mixture was set aside at −20 °C for 17 h. The mixture was then warmed to room temperature, diluted with water, and extracted with ether; the extracts after washing, *etc.*, gave an oil which after p.l.c. (n-hexane–ether, 2 : 1) gave the *dithian* (15c) (78 mg, 33%) (Found: *M*, 476.201. $C_{26}H_{36}O_4S_2$ requires *M*, 476.205). Mercuric oxide (21.6 mg, 0.1 mmol) was stirred in tetrahydrofuran–15% water (1 cm^3); boron trifluoride etherate (25.4 mg) was added, and then the dithian (23.7 mg, 0.05 mmol) in tetrahydrofuran (1 cm^3) during 10 min. The mixture was stirred at room temperature for 70 h. The solvent was evaporated and the residue purified by p.l.c. (n-hexane–ether, 1 : 1) to give the title ketone (15d) (14.1 mg, 73%) as an oil (one spot on t.l.c.) (Found: *M*, 386.204. $C_{23}H_{30}O_5$ requires *M*, 386.209).

Reactions of 2-(2-p-*Benzyloxyphenylethyl*)-1,3-*dithian with n-Butyl-lithium.*—The title dithian (236 mg, 0.714 mmol) in tetrahydrofuran (1 cm^3) was cooled to −35 °C. Under a nitrogen atmosphere was added n-butyl-lithium (0.75 mmol, 2M hexane solution) and tetrahydrofuran (1 cm^3). A deep red solution formed, fading to pale yellow after 4 h. A portion (0.5 cm^3) was withdrawn and quenched with D_2O. The organic products were isolated through ether extraction and separated by p.l.c. (n-hexane–ether, 2 : 1). At highest R_F was found *cis,trans*-1,2,3-triphenylcyclopropane (20) (1.3 mg), m.p. 63—65 °C (lit.,[38] m.p. 63—64 °C) (Found: *M*, 270. Calc. for $C_{21}H_{18}$; *M*, 270); at intermediate R_F was starting dithian, by t.l.c. and n.m.r. comparison with authentic sample; and at lowest R_F was 2-(2-*p*-hydroxyphenylethyl)-1,3-dithian, from n.m.r. data. To the residue (1.5 cm^3) was added methyl iodide (112 mm^3), and the solution warmed to room temperature. Isolation of products through chloroform extraction and p.l.c. (n-hexane–ether, 2 : 1) gave 1,2,3-triphenylcyclopropane (2.6 mg). At intermediate and lowest R_F were found small samples of 1-*p*-methoxyphenyl)-4,8-dithianon-2-ene (21b) and 1-(*p*-hydroxyphenyl)-4,8-dithianon-2-ene (21a), the structures of which were assigned from [1] H.m.r. and mass-spectral data.

Preparation of Ketones via *Trialkylcyanoborates.*—(*a*) A solution of diborane in tetrahydroforum (1.6M, 4.0 cm^3) was cooled to 0 °C, and 2,3-dimethylbut-2-ene (0.57 g, 6.8 mmol) was added. The mixture was stirred for 1 h at 0 °C. *p*-Methoxystyrene [0.76 g, 6 mmol, prepared (63%) by copper-catalysed decarboxylation of *p*-methoxycinnamic acid] was added and the reaction continued for 0.5 h. Then 4-(*p*-methoxyphenyl)but-1-ene (0.94 g, 6 mmol, prepared from allylmagnesium bromide and anisyl chloride in ether at 0 °C over 3 h, 79%) was introduced and reaction continued for 2 h. The solution was then stirred into a suspension of powdered sodium cyanide (0.64 g, 13.2 mmol) in tetrahydrofuran, and stirring continued for 1 h while the reaction temperature rose to 22 °C. The mixture was cooled to −78 °C, trifluoroacetic anhydride (2.6 g, 15.5 mmol) was added, and the reactants allowed to reach room temperature over 1 h. Finally, oxidation of the organoboranes was conducted with hydrogen peroxide (16 cm^3, 100 vol.) and aqueous sodium hydroxide (14.4 cm^3, 3M), stirring for 3 h at 22 °C and 0.5 h at 50 °C. The products were isolated by ether extraction. The extracts after standard treatment gave an oil from which a ketonic fraction (0.5 g) was separated by p.l.c. (chloroform). This was shown to be a *ca.* equimolar mixture of 1,7-bis-(*p*-methoxyphenyl)heptan-3-one (15b), 1,5-bis-(*p*-methoxyphenyl)pentan-3-one (24), and 1,9-bis-(*p*-methoxyphenyl)-nonan-5-one (25), by g.l.c. (5-ft × 0.25-in glass column packed with 3% trifluoropropylmethylsilicone fluid on 100—120 Diatomite CQ, at 200 °C; at 60 cm^3 min^{-1}, retention times were 34, 17, and 71 min, respectively, for the three ketones) using authentic specimens for comparison, and by mass spectrometry.

(*b*) A similar procedure to that in (*a*), using 2,3-dimethylbut-2-ene (0.29 g, 3.4 mmol) and *p*-methoxyphenylstyrene (0.76 g, 6 mmol) gave an authentic sample of 1,5-*bis*-(*p*-*methoxyphenyl*)*pentan*-3-*one* (0.16 g, 18% after p.l.c.), one peak on g.l.c. (Found: *M*, 298.159. $C_{19}H_{22}O_3$ requires *M*, 298.157). Repetition of the preparation with 4-(*p*-methoxyphenyl)but-1-ene provided authentic 1,9-*bis*-(p-*methoxyphenyl*)*nonan*-5-*one* (25% after p.l.c.), one peak on g.l.c. (Found: *M*, 354.219. $C_{23}H_{30}O_3$ requires *M*, 354.220).

Catalytic Debenzylations.—(*a*) 1-(4-Benzyloxyphenyl)-7-(2-benzyloxy-3,4-dimethoxyphenyl)heptan-3-one (1 g) in acetic acid (40 cm^3) was injected into acetic acid (20 cm^3) containing 5% palladium–carbon (1 g), pre-saturated with hydrogen, and the mixture stirred under hydrogen until 2 mol equiv. were absorbed. After filtration, the solvent was evaporated and the residue dissolved in ether. The solution was washed, evaporated, and the residue separated by p.l.c. (n-hexane–ether, 1 : 3). The major product crystallised from ethyl acetate–n-hexane to provide 1-(4-*hydroxyphenyl*)-7-(2-*hydroxy*-3,4-*dimethoxyphenyl*)*heptan*-3-*one* (11e), m.p. 71—72 °C (356 mg, 53%) (Found: *M*, 358.150. $C_{21}H_{26}O_5$ requires *M*, 358.178). Interruption of one experiment before complete hydrogenolysis gave the same dihydroxy-compound together with 1-(4-*benzyloxyphenyl*)-7-(2-*hydroxy*-3,4-*dimethoxyphenyl*)*heptan*-3-*one* (11f), m.p. 80—81 °C from n-hexane (Found: C, 74.55; H, 7.2. $C_{28}H_{32}O_5$ requires C, 75.00; H, 7.15%).

(*b*) 1-(4-Benzyloxyphenyl)-7-(2-benzyloxy-3,4-dimethoxyphenyl)heptan-3-ol (1.26 g) was hydrogenolysed in acetic acid (40 cm^3) over 10% palladium–carbon (400 mg) until 2 mol equiv. were absorbed. Product isolation as above gave 1-(4-*hydroxyphenyl*)-7-(2-*hydroxy*-3,4-*dimethoxyphenyl*)-*heptan*-3-*ol* (11d) (630 mg, 74%), as a viscous oil (Found: M^+, 360.191. $C_{21}H_{28}O_5$ requires *M*, 360.195).

[9/580 *Received*, 12*th April*, 1979]

REFERENCES

[1] E. Vogel and S. Pelletier, *J. Pharm.*, 1815, **2**, 50.
[2] V. Lampe, J. Milobedzka, and St. v. Kostanecki, *Ber.*, 1910, **43**, 2163.
[3] K. R. Srinivasan, *J. Pharm. Pharmacol.*, 1953, **5**, 448.

[4] N. Nomura and T. Tokoroyama, *J.C.S. Chem. Comm.*, 1974, 65; 1975, 316.
[5] T. Suga, Y. Asakawa, and N. Iwata, *Chem. and Ind.*, 1971, 766; N. I. Uvarova, G. I. Oshitok, A. K. Dzizenko, and G. B. Elyakov, *Khim. prirod. Soedinenii*, 1970, 463.
[6] H. Sasatani and G. Izumiya, *Research Bulletin of the College Experimental Forests*, College of Agriculture, Hokkaido University, Japan, 1974, **31**, 23; M. Terasawa, T. Koga, H. Okuyama, and M. Miyake, *J. Japan. Wood Res. Soc.*, 1973, **19**, 45, 47.
[7] J. J. Karchesy, M. L. Laver, D. F. Barofsky, and E. Barofsky, *J.C.S. Chem. Comm.*, 1974, 649.
[8] Y. Asakawa, F. Genjida, S. Hayashi, and T. Matsuura, *Tetrahedron Letters*, 1969, 3235; Y. Asakawa, *Bull. Chem. Soc. Japan*, 1970, **43**, 2223.
[9] I. L. deAlbuquerque, C. Galeffi, C. G. Casinovi, and G. B. Marini-Bettolo, *Gazetta*, 1964, **94**, 287; A. Aragao Craveiro, A. da Costa Prado, O. R. Gottlieb, and P. C. Welerson de Albuquerque, *Phytochemistry*, 1970, **9**, 1869.
[10] M. J. Begley and D. A. Whiting, *Chem. Comm.*, 1970, 1207; R. V. M. Campbell, L. Crombie, B. Tuck, and D. A. Whiting, *Chem. Comm.*, 1970, 1206; M. J. Begley, R. V. M. Campbell, L. Crombie, B. Tuck, and D. A. Whiting, *J. Chem. Soc.* (*C*), 1971, 3634.
[11] M. Yasue, *J. Japan Wood Res. Soc.*, 1965, **11**, 146, 153; M. Yasue and H. Imamura, *ibid.*, 1966, **12**, 226, 231.
[12] T. Anthonsen, G. B. Lorentzen, and K. E. Malterud, *Acta Chem. Scand.*, 1975, **B29**, 529.
[13] K. E. Malterud, T. Anthonsen, and J. Hjortas, *Tetrahedron Letters*, 1976, 3069.
[14] M. Nagai, M. Kubo, M. Fujita, T. Inoue, and M. Matsuo, *J.C.S. Chem. Comm.*, 1976, 338.
[15] J. M. Edwards and U. Weiss, *Phytochemistry*, 1970, **9**, 1653; 1974, **13**, 1597.
[16] R. G. Cooke and W. Segal, *Austral. J. Chem.*, 1955, **8**, 107, 413; I. R. C. Bick and A. J. Blackman, *ibid.*, 1973, **26**, 1377.
[17] T. Cremona and J. M. Edwards, *Lloydia*, 1974, **37**, 112.
[18] J. M. Edwards, *Phytochemistry*, 1974, **13**, 290.
[19] R. G. Cooke and R. L. Thomas, *Austral. J. Chem.*, 1975, **28**, 1053.
[20] R. Thomas, *Biochem.*, 1961, **78**, 807; *Chem. Comm.*, 1971, 739; J. M. Edwards and U. Weiss, *Tetrahedron Letters*, 1969, 4325; J. M. Edwards, R. C. Schitt, and U. Weiss, *Phytochemistry*, 1972, **11**, 1717; A. D. Harmon and J. M. Edwards *Tetrahedron Letters*, 1977, 4471.
[21] A. C. Bazan, J. M. Edwards, and U. Weiss, *Tetrahedron Letters*, 1977, 147.
[22] P. J. Roughley and D. A. Whiting, *Tetrahedron Letters*, 1971, 3741; *J.C.S. Perkin I*, 1973, 2379.
[23] H. J. J. Pabon, *Rec. Trav. chim.*, 1964, **83**, 379.
[24] R. D. Rieke and S. E. Bales, *J.C.S. Chem. Comm.*, 1973, 879; *J. Amer. Chem. Soc.*, 1972, **94**, 7178.
[25] A. I. Meyers and E. M. Smith, *J. Org. Chem.*, 1973, **38**, 36.
[26] M. Charpentier-Morize and P. Colard, *Bull. Soc. chim. France*, 1962, 1982.
[27] G. Hesse and H. Witte, *Angew. Chem.*, 1963, **75**, 791; *Annalen*, 1965, **687**, 1; G. Hesse, H. Witte, and G. Bittner, *ibid.*, 1965, **687**, 9; G. Hesse, H. Witte, and W. Gulden, *Tetrahedron Letters*, 1964, 405; E. Behm, A. Haag, G. Hesse, and H. Witte, *Annalen*, 1970, **737**, 70; A. Pelter, M. G. Hutchings, and K. Smith, *J.C.S. Chem. Comm.*, 1970, 1529; *J.C.S. Perkin II*, 1975, 129; A. Pelter, M. G. Hutchings, K. Smith, and K. Rowe, *J.C.S. Chem. Comm.*, 1971, 1048.
[28] H. C. Brown, E. Negishi, and J. Katz, *J. Amer. Chem. Soc.*, 1975, **97**, 2791; E. Negishi and H. C. Brown, *Synthesis*, 1974, 77; C. F. Lane and H. C. Brown, *J. Organometallic Chem.*, 1972, **34**, C29; Y. Yamamoto, K. Kondo, and I. Moritari, *Tetrahedron Letters*, 1974, 793; H. C. Brown, J. Katz, C. F. Lane, and E. Negishi, *J. Amer. Chem. Soc.*, 1975, **97**, 2799.
[29] E. Chapman, A. G. Perkin, and R. Robinson, *J. Chem. Soc.*, 1927, 3027.
[30] P. C. Mitter and S. De, *J. Indian Chem. Soc.*, 1939, 35.
[31] F. Krollpfeiffer and W. Schäfer, *Ber.*, 1923, **56**, 620.
[32] R. Baird and S. Winstein, *J. Amer. Chem. Soc.*, 1962, **84**, 788.
[33] E. D. Bergmann and M. Sulzbacher, *J. Org. Chem.*, 1951, **16**, 84.
[34] D. G. Doherty, *J. Amer. Chem. Soc.*, 1955, **77**, 4887.
[35] Mme. Ramart-Lucas and Mlle. Amagat, *Comptes rend.*, 1929, **188**, 638.
[36] 'Dictionary of Organic Compounds,' Eyre and Spottiswoode, London, 1965.
[37] E. J. Corey and B. W. Erickson, *J. Org. Chem.*, 1971, **36**, 3553.
[38] L. I. Zakharkin and L. A. Savina, *Zhur. obshchei Khim.*, 1967, **37** (11), 2565 (*Chem. Abs.*, 1968, **68**, 104,629g).