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AN APPROACH TO THE BIOMIMETIC SYNTHESIS OF ARYLTETRALIN LIGNANS

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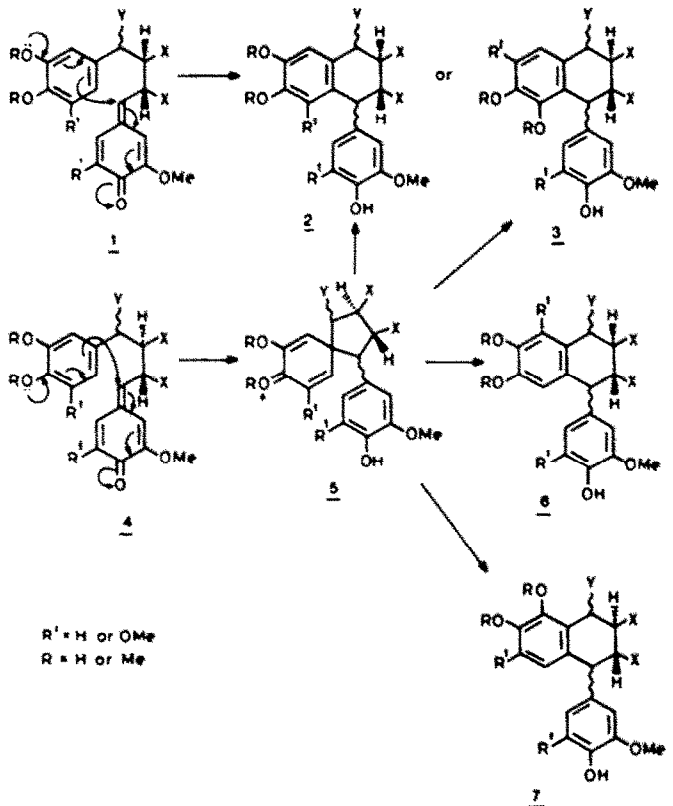
Abstract -The BF_3 catalysed cyclisation of 3-arylpropyl substituted quinone-methide ketals affords a mild, biomimetic route to aryltetralins. ^1H- and ^{13}C-NMR spectra of the products are reported.

Two possible routes which can be envisaged for the biogenesis of aryltetralin lignans are shown in Scheme 1.[1] The first involves direct intramolecular cyclisation of a quinone-methide **1** by nucleophilic attack of an electron rich aromatic ring onto the conjugated dienone system. The second involves the formation and rearrangement of a spirodienone intermediate **5**.[2] Indirect evidence for the operation of the latter route is provided by the natural occurrence of lignans such as cycloolivil **8** and lyoniresinol **9** having an OH group at C-7 and lignans such as α- and β-peltatin **10** having an oxygen substituent at C-5,[3] the formation of which can be most reasonably accounted for by this route.

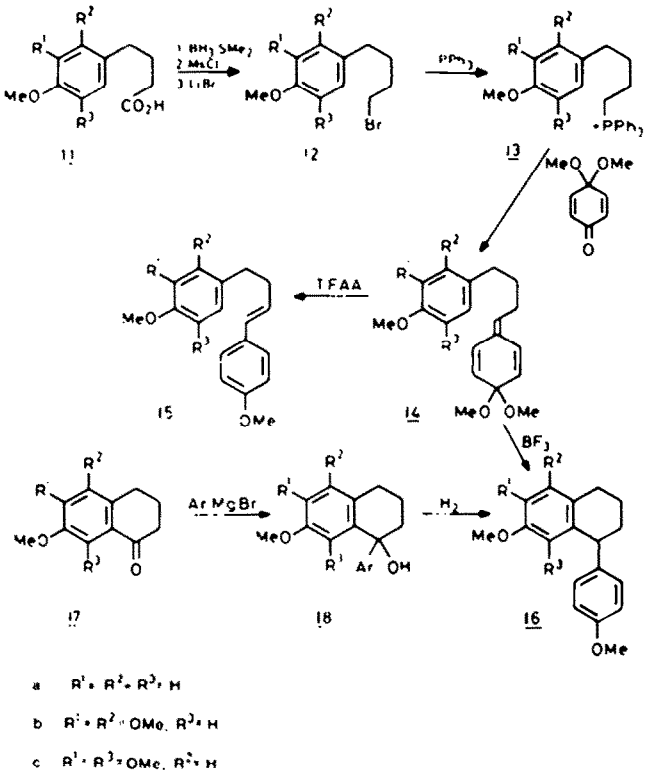
In order to investigate the feasibility of at least one of these routes we have prepared a series of model compounds **14** and studied their cyclisation using Lewis acid catalysts.[4]

The quinone-methide ketals **14** were prepared from the corresponding 4-arylbutanoic acids **11**[5-7] as shown in Scheme 2. The acids were reduced using borane-dimethyl sulphide[8] to give the corresponding alcohols. Mesylation using methanesulphonyl chloride and triethylamine followed by treatment with lithium bromide in acetone gave the 4-arylbutyl bromides **12**.[9] Quaternisation with triphenylphosphine gave the phosphonium salts **13** which were subjected to a Wittig reaction with 4,4-dimethoxycyclohex-2,5-dienone[10,11] to give the required quinone-methide ketals **14**.

Treatment of **14a** with trifluoracetic anhydride gave a product which was identified on the basis of its ^1H-NMR and mass spectra as the alkene **15a**. However, treatment with BF_3-etherate gave a new product which was identified on the basis of its ^1H- and ^{13}C-NMR and mass spectra as the aryltetralin **16a**. The mass spectra of **15a** and **16a** readily distinguish between the two isomers since while **15a** shows intense ions corresponding to benzylic and allylic cleavage ($Ar^1CH_2^+$ and $Ar^2CH{=}CHCH_2^+$) compound **16a** in contrast shows



Scheme 1.

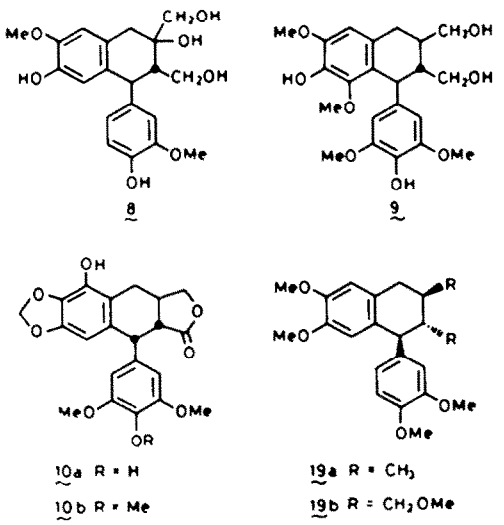


Scheme 2.

an intense ion corresponding to loss of the pendant aryl group and an intense molecular ion (Table 3). The identification of the aryltetralin was further aided by the close similarity of its ^{1}H- and ^{13}C-NMR spectra with those of the known compounds **19a** and **19b** (Tables 1 and 2). However, the identification was confirmed beyond doubt by carrying out an independent unambiguous synthesis of **16a** starting from the tetralone **17a** (Scheme 2).

Similarly, treatment of the quinone-methide ketals **14b** and **14c** with BF_3-etherate gave the aryltetralins **16b** and **16c**, while treatment of **14b** with TFAA gave a mixture of the aryltetralin **16b** and the elimination product **15b**. The structure of the aryltetralin **16b** was again confirmed by carrying out an independent synthesis starting from the corresponding tetralone **17b**.

These reactions constitute a new route to aryltetralins and demonstrate the feasibility of this approach to a biomimetic synthesis of these compounds.



EXPERIMENTAL

IR and UV spectra were recorded on Pye Unicam SP1050 and Perkin Elmer 402 spectrometers respectively. ^{1}H- and ^{13}C-NMR spectra were recorded on Varian HA100 and XL100 instruments using tetramethylsilane as internal standard. Mass spectra were obtained on an A.E.I. MS9 double focusing instrument operating at 250° and 70 eV.

4-(4-Methoxyphenyl)butanoic acid **11a**. Prepared according to the lit. procedure from methoxybenzene and succinic anhydride followed by Clemmensen reduction[5,6] m.p. 60° (lit.[5,6] 61–62°). 84% overall yield.

Ethyl 4-oxo-4-(2,3,4-trimethoxyphenyl)butanoate. To a soln of stannic chloride (13.4 ml) in dry CH_2Cl_2 (20 ml) stirring at 0° was added dropwise a soln of 1,2,3-trimethoxybenzene (10 g) and ethyl succinoyl chloride (5.1 ml) in CH_2Cl_2 (25 ml) over a period of 1 hr. Cooling was continued for a further 4 hr and the mixture left stirring overnight and then poured into a mixture of ice and dil HCl. The organic phase was separated, washed with $NaHCO_3$ aq and dried over $MgSO_4$. The solvent was removed *in vacuo* to leave a thick oil which solidified on standing (11 g) and was used in the next step without further purification. ν_{max}^{film} 1740, 1680 cm^{-1}. *m/e* 296 (M^+, 6%) 251 (3), 223 (2), 195 (49), 168 (100), 153 (57), 125 (27), 110 (34). δ $CDCl_3$ 1.23t (7), 2.67t (7), 3.27t (7), 3.82s (3H), 3.84s (3H), 3.95s (3H), 4.10q (7), 6.68d (8), 7.50d (8).

4-Oxo-4-(2,3,4-trimethoxyphenyl)butanoic acid. The crude product from the above reaction was refluxed with 8%

Table 1. ^{1}H-NMR data

Proton	19a[12]	19b[12]	16a	16b	16c
1	3.43d (10)	4.0d (9)	4.0m	3.9m	3.7m
2/3	1.4–1.7m	1.5–2.4m	0.7–2.2m	0.7–2.1m	0.7–2.1m
4	2.70m	2.7–3.0m	2.76br t (6)	2.71br t (6)	2.6m
8	6.16s	6.25s	6.37d (2)	6.16s	–
5	6.55–6.85m	6.55–6.85m	6.6–7.1m		6.39s
ArH				6.6–7.1m	6.78AB
OMe	3.55s	3.27s	3.58s	3.59s	3.69s
	3.79s	3.35s	3.72s	3.75s	3.80s
	3.82s	3.58s		3.83s	
	3.96s	3.80s		3.86s	–
		3.83s	–		–
		3.88s	–	–	

Table 2. ^{13}C-NMR data

Carbon	19a[12]	19b[12]	16a	16b
1	54.37	47.29	45.06	44.77
2	43.87	44.93	28.95	23.30
3	35.62	36.40	21.12	20.12
4	39.08	33.11	33.30	33.08
4a	129.16	128.93	139.44	124.14
5	110.77	111.15	129.74	140.33
6	147.16	147.22	114.82	135.18
7	147.45	147.50	157.52	150.96
8	113.01	112.96	112.31	109.05
8a	139.11	138.09	140.78	139.43
1′	132.54	132.14	129.74	129.32
2′	112.26	112.42	129.66	129.65
3′	148.98	148.96	113.68	113.65
4′	147.03	147.08	157.86	157.88
5′	110.86	110.98	113.68	113.65
6′	122.00	121.83	129.66	129.65
OMe	55.92	55.85 (×4)	55.11	55.20
	55.84 (×3)	58.91	55.16	55.87
				60.34
				60.77

Table 3. Mass spectral data

Ion	15a	15b	16a	16b	16c
M^+	268 (11)	328 (66)	268 (57) (49)	328 (25) (95)	328 (29)
$Ar^2CH{=}CHCH_2^+$	147 (100)	147 (11)	147 (3) (5)	147 (3) (4)	147 (3)
$Ar^1CH_2^+$	121 (65)	181 (71)	121 (16) (44)	181 (57) (5)	181 (48)
$M-Ar^{2\cdot}$	161 –	221 (5)	161 (16) (22)	221 (2) (29)	221 (31)
$M-Ar^2H^+$	160 –	220 (9)	160 (100) (100)	220 (3) (17)	220 (9)
$Ar^2CH_2^+$	121 (65)	121 (22)	121 (16) (44)	121 (11) (51)	121 (24)
$Ar^2CH{=}CH_2^+$	134 (15)	134 (4)	134 (15) (34)	134 (1) (10)	134 (2)
$M-Ar^2CH{=}CH_2^+$	134 (15)	194 (60)	134 (15) (34)	194 (2) (11)	194 (9)

alcoholic alkali for 3 hr. Excess alcohol was evaporated, the product diluted with water and extracted with ether. The aqueous alkaline soln was acidified with HCl, extracted with ether and the organic layer dried over $MgSO_4$ and evaporated to give an oil which solidified on standing (5.6 g, 35% from trimethoxybenzene) m.p. 88–89°. δ $CDCl_3$ 2.73t (6) (2H), 3.30t (6) (2H), 3.84s (3H), 3.88s (3H), 3.96s (3H), 6.70d (9) (1H), 7.52d (9) (1H), 9.73br s (1H). *m/e* 268 (M^+, 14%) 195 (100). ν_{max} 1714, 1671 cm^{-1}.

4-(2,3,4-Trimethoxyphenyl)butanoic acid **11b**. To amalgamated Zn (25 g) was added water (16 ml), conc HCl (36 ml), toluene (26 ml) and the above keto-acid (11.8 g) and the mixture refluxed for 48 hr, adding conc HCl (5 ml) every 6–8 hr. The soln was cooled to room temp, the aqueous layer separated and after dilution with water (50 ml) extracted with ether (3 × 25 ml). The organic extracts were combined and added to 5% NaOH aq and the solvents removed by steam distillation. The residual alkaline soln was cooled to 80° and

treated with dimethyl sulphate (15 ml) to remethylate demethylated material. After stirring for 30 min the aqueous soln was treated with activated charcoal and filtered. The filtrate was cooled to 19° and acidified with conc HCl. The acid which separated was extracted into ether and concentration of the ether soln yielded the crude acid (9.4 g, 86%). ν_{max}^{film} 1716 cm^{-1}. δ $CDCl_3$ 1.95m (2H), 2.27t (6) (2H), 2.62t (7) (2H), 3.82s (3H), 3.84s (3H), 3.86s (3H), 6.56d (8) (1H), 6.82d (8) (1H). *m/e* 254 (M^+, 48%), 181 (100), 167 (13), 166 (27), 136 (18).

Methyl 4-(3,4,5-trimethoxyphenyl)butanoate. Prepared according to the procedure described by Evans *et al.* 54% overall yield from 3,4,5-trimethoxycinnamic acid. ν_{max}^{film} 1740, 1590 cm^{-1}. δ $CDCl_3$ 1.93m (2H), 2.30m (2H), 2.52m (2H), 3.60s (3H), 3.82s (9H), 6.40s (2H).

4-(3,4,5-Trimethoxyphenyl)butanoic acid **11c**. The methyl ester (2.1 g) and KOH (0.7 g) in EtOH (10 ml) containing water (1 ml) were refluxed for 3 hr. Excess alcohol was evaporated, the mixture diluted with water, and the aqueous extract acidified with HCl (2 ml). The mixture was cooled in ice and the product extracted into ether, washed with brine, dried ($MgSO_4$) and evaporated to afford the acid which was recrystallised from ether. m.p. 77–78° (1.84 g, 92%). ν_{max}^{film} 1715, 1595, 1454, 1425, 1240, 1130 cm^{-1}. δ $CDCl_3$ 1.8–2.8 m (6H), 3.85s (9H), 6.40s (2H). Found: C, 59.59; H, 6.86. $C_{13}H_{18}O_5$ requires: C, 61.02; H, 7.08. *m/e* (M^+, 88%), 195 (10), 181 (100), 179 (30), 151 (11). Acc. Mass M^+ 254.1152 ($C_{13}H_{18}O_5$).

4-(4-Methoxyphenyl)butan-1-ol. 4-(4-Methoxyphenyl)-butanoic acid (3.8 g, 20 mM) was dissolved in dry ether and borane–dimethyl sulphide (2.4 ml, 10 M soln, 23 mM) added dropwise under nitrogen. The mixture was refluxed gently for 1 hr after which it was cooled to room temp and treated slowly with MeOH (1.5 ml) before being finally poured into ice-cold MeOH (60 ml). Removal of the solvents *in vacuo* gave the product alcohol as a thick oil (3.5 g, 96%). ν_{max}^{film} 3100 3600 cm^{-1}. δ $CDCl_3$ 1.60m (4H), 2.30br s (1H, D_2O exch.), 2.60m (2H), 3.60m (2H), 3.80s (3H), 6.80d (9) (2H), 7.10d (9) (2H), 7.10d (9) (2H). *m/e* 180 (M^+, 43%), 134(20), 121(100).

4-(4-Methoxyphenyl)butyl methanesulphonate. To the alcohol (1.09 g, 6 mM) in dry ether (50 ml) at 0° was added with stirring Et_3N (4.2 ml, 30 mM) followed by methanesulphonyl chloride (1.4 ml, 18 mM). The mixture was allowed to warm to room temp and the stirring continued for 3 hr when the mixture was poured into ether (200 ml), extracted with water (2 × 50 ml) and sat $NaHCO_3$ aq (2 × 20 ml) and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* gave the crude mesylate which was used without further purification (1.45 g, 100%). δ $CDCl_3$ 1.70m (4H), 2.60m (2H), 2.94s (3H), 3.70s (3H), 4.20m (2H), 6.80d (8) (2H), 7.10s (8) (2H). ν_{max}^{film} 1180, 1360 cm^{-1}.

4-(4-Methoxyphenyl)butyl bromide **12a**. To the crude mesylate (1.45 g, 6 mM) was added acetone (50 ml) and lithium bromide (1.6 g, 18 mM). The mixture was refluxed for 6 hr, evaporated *in vacuo*, taken up in ether (200 ml), washed with brine (2 × 50 ml) and dried ($MgSO_4$). The solvent was removed *in vacuo* to give a pale yellow oil (1.25 g, 86% based on the alcohol). δ $CDCl_3$ 1.78m (4H), 2.54t (7) (2H), 3.34t (6) (2H), 3.72s (3H), 6.77d (8) (2H), 7.04d (8) (2H). *m/e* 242/244 (M^+, 6%), 121 (100).

4-(2,3,4-Trimethoxyphenyl)butan-1-ol. This compound was prepared by borane–methylsulphide reduction of the acid **11b** using the same procedure as described above for the preparation of 4-(4-methoxyphenyl)butan-1-ol. ν_{max}^{film} 3200–3600 cm^{-1}. δ $CDCl_3$ 1.60m (4H), 2.60m (2H), 3.00br (1H, D_2O exch.), 3.60m (2H), 3.82s (3H), 3.84s (3H), 3.86s (3H), 6.56d (8) (1H). *m/e* 240 (M^+, 38%), 181 (100), 166 (27), 136 (13).

4-(2,3,4-Trimethoxyphenyl)butyl methanesulphonate. This was prepared from the above alcohol using the same procedure as described for 4-(4-methoxyphenyl)butyl methanesulphonate. ν_{max}^{film} 1180, 1360 cm^{-1}. δ $CDCl_3$ 1.73m (4H), 2.60m (2H), 3.00s (3H), 3.86s (9H), 4.22m (2H), 6.55d (8) (1H), 6.80d (8) (1H).

4-(2,3,4-Trimethoxyphenyl)butyl bromide **12b**. This was prepared from the above mesylate using the same procedure as described for the preparation of **12a**. The bromide was obtained as a pale yellow oil (86%). δ $CDCl_3$ 1.80m (4H), 2.57t (7) (2H), 3.40t (6) (2H), 3.80s (3H), 3.83s (3H), 3.85s (3H), 6.56d (9) (1H), 6.78d (9) (1H). *m/e* 302/4 (M^+, 22%), 181 (100), 166 (21). Acc. Mass M^+ 302.0534 ($C_{13}H_{19}BrO_3$).

4-(3,4,5-Trimethoxyphenyl)butan-1-ol. This compound was prepared by borane methylsulphide reduction of the acid **11c** using the same procedure as employed for the preparation of 4-(4-methoxyphenyl)butan-1-ol. ν_{max}^{film} 3200–3600, 1595, 1465, 1240, 1130 cm^{-1}. δ $CDCl_3$ 1.64m (4H), 2.35br (1H, D_2O exch.), 2.57m (2H), 3.64m (2H), 3.79s (3H), 3.81s (6H), 6.40s (2H). *m/e* 240 (M^+, 12%), 182 (13), 181 (25), 136 (12), 121 (12), 111 (12), 108 (12), 107 (15).

4-(3,4,5-Trimethoxyphenyl)butyl methanesulphonate. This was prepared from the above alcohol using the same procedure as described for 4-(4-methoxyphenyl)butyl methanesulphonate. ν_{max}^{film} 1595, 1355, 1245, 1175, 1130 cm^{-1}. δ $CDCl_3$ 1.75m (4H), 2.60m (2H), 3.00s (3H), 3.85s (9H), 4.25m (2H), 6.40s (2H).

4-(3,4,5-Trimethoxyphenyl)butyl bromide **12c**. This was prepared from the above mesylate using the same procedure as described for the preparation of **12a** (86% yield). δ $CDCl_3$ 1.84m (4H), 2.58t (7) (2H), 3.41t (6) (2H), 3.81s (3H), 3.83s (6H), 6.40s (2H). *m/e* 302/4 (M^+, 25%), 215 (10), 181 (100). Acc. Mass M^+ 302.0515 ($C_{13}H_{19}BrO_3$).

4-(4-Methoxyphenyl)butyl triphenylphosphonium bromide **13a**. A mixture of the bromide **12a** (1.22 g, 5 mM), triphenylphosphine (1.13 g, 5 mM) and dry benzene (5 ml) was heated under reflux for 20 hr. After cooling the upper benzene layer was decanted to leave a heavy transparent glass which was washed well with dry benzene to remove the starting materials and triturated with dry benzene and dry petroleum ether (b.p. 60–80°) to give a hard gummy mass which resisted all attempts at recrystallisation. After drying in a vacuum desiccator the product was obtained as an amorphous powder which was extremely hygroscopic (yield 80%) m.p. 160–161°. δ $CDCl_3$ 1.4–2.1m (4H), 2.59br t (6) (2H), 3.66m (2H), 3.70s (3H), 6.70d (8) (2H), 7.02d (8) (2H), 7.68m (15H).

4-(2,3,4-Trimethoxyphenyl)butyl triphenylphosphonium bromide **13b**. This was prepared using the same procedure as for compound **13a**. The salt was obtained as an amorphous hygroscopic powder (90%). δ $CDCl_3$ 1.85m (4H), 2.60m (2H), 3.80m (2H), 3.80s (9H), 6.55d (8) (1H), 7.70m (15H).

4-(3,4,5-Trimethoxyphenyl)butyl triphenylphosphonium bromide **13c**. This was prepared using the same procedure as for **13a**. The salt was obtained as an amorphous hygroscopic powder (85%). δ $CDCl_3$ 1.5–2.2m (4H), 2.67m (2H), 3.24m (2H), 3.74s (3H), 3.78s (6H), 6.50s (2H), 7.70m (15H).

4,4-Dimethoxycyclohexa-2,5-dienone. Prepared according to the lit. procedure[11] from 4-methoxyphenol by oxidation with thallium trinitrate (98% yield). ν_{max}^{film} 1643 and 1695 cm^{-1}. δ $CDCl_3$ 3.35s (6H), 6.20d (10) (2H), 6.80d (10) (2H).

Preparation of quinone-methide ketal **14a**. To a suspension of the phosphonium salt **13a** (0.976 g, 2 mM) in THF (20 ml) under N_2 at −25° was added n-BuLi (3 ml, 1.39 M soln, 4 mM). The temperature was maintained at −25° for 15 min and the mixture then allowed to warm to room temp. To the resulting red soln was added a soln of 4,4-dimethoxycyclohexa-2,5-dienone (0.308 g, 2 mM) in THF (1 ml). The mixture was stirred for 2 hr and then poured into CH_2Cl_2 (50 ml) and 50/50 saturated brine/water (25 ml). The organic layer was separated and dried ($MgSO_4$). Removal of the solvent *in vacuo* yielded a brown oil (0.850 g). Attempted purification of a small amount of this crude product on a column of neutral alumina (70–230 mesh) eluted with CH_2Cl_2 gave a low yield (14%) of a compound tentatively identified as the alkene **15a** ν_{max}^{film} 1615, 1520, 1250, 1180, 1035 cm^{-1}. δ $CDCl_3$ 1.2–1.8m (4H), 3.74s (6H), 5.9–6.4m (1H), 6.7–7.3m (9H). *m/e* 368 (M^+, 17%), 147 (100), 134 (20), 121 (71). Acc. Mass M^+ 238.1466 ($C_{18}H_{20}O_2$).

Preparation of quinone-methide ketal **14b**. Prepared by Wittig reaction of the phosphonium salt with 4,4-dimethoxycyclohexa-2,5-dienone as described for the preparation of **14a**. The crude ketal was obtained as brown viscous oil and used without further purification.

Preparation of quinone-methide ketal **14c**. Prepared by Wittig reaction of the phosphonium salt with 4,4-

dimethoxycyclohexa-2,5-dienone as described for the preparation of **14a**. The crude ketal was obtained as a brown viscous oil and used without further purification.

Reaction of quinone-methide ketal **14a** *with* BF_3*-etherate.* To a soln of the crude quinone-methide ketal (600 mg) in CH_2Cl_2 (8 ml) was added BF_3-etherate (2.1 ml) and the mixture kept stirring at room temp for 15 hr. The mixture was then poured into CH_2Cl_2 (30 ml) and washed with sat $NaHCO_3$ aq (30 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product (550 mg) which showed two distinct spots on TLC in addition to some baseline material. Separation of the EtOAc soluble material by flash chromatography on silica gel (400–230 mesh) eluting with EtOAc yielded two products:

(i) 1-(4-Methoxyphenyl)-7-methoxytetralin **16a** (230 mg, 42%) ν_{max}^{film} 1615, 1518, 1250, 1040 cm^{-1}. For ^1H- and ^{13}C-NMR spectra see Tables 1 and 2. *m/e* 268 (M^+, 57%), 240 (13), 209 (12), 160 (100), 159 (14), 134 (15), 121 (16). M^+ 268.1454 ($C_{18}H_{20}O_2$).

(ii) Triphenylphosphine oxide (200 mg) m.p. 156–156.5°. *m/e* 277 (M^+, 100%), 149 (91). In addition 120 mg of material which was insoluble in ethyl acetate and having a low R_f separated whose NMR strongly resembled that of the starting phosphonium salt.

Reaction of quinone-methide ketal **14b** *with* BF_3*-etherate.* To a soln of the crude quinone-methide ketal (1.2 g) in CH_2Cl_2 (10 ml) was added BF_3-etherate (3.5 ml). The mixture was stirred at room temp for 30 min and then diluted with CH_2Cl_2 (80 ml), washed with sat $NaHCO_3$ aq (2 × 25 ml) and dried ($MgSO_4$). On concentration *in vacuo* a brown viscous mass was obtained (1.11 g) which showed two major spots on TLC along with a small amount of baseline material. This was further purified by flash chromatography on silica gel (230–400 mesh) eluting with EtOAc to afford 2 products (i) 1-(4-methoxyphenyl)-5,6,7-trimethoxytetralin **16b** (0.484 g, 44°). For ^1H- and ^{13}C-NMR spectra see Tables 1 and 2. *m/e* 328 (M^+, 28%), 181 (57), 166 (13), 158 (10), 143 (20), 124 (100), 121 (12), 109 (93). M^+ 328.1669 ($C_{20}H_{24}O_4$ requires 328.1672). (ii) Triphenylphosphine oxide (0.375 g, 36%).

Reaction of quinone-methide ketal **14c** *with* BF_3 *etherate.* To a soln of the crude quinone-methide ketal (0.72 g) in CH_2Cl_2 (10 ml) was added BF_3-etherate (2.5 ml) at room temp. The mixture was stirred for 30 min and then poured into a 1:1 mixture of CH_2Cl_2 and brine (50 ml). The organic layer was separated and washed with water (25 ml), sat $NaHCO_3$ aq (25 ml), dried and evaporated to give a brown gum (0.60 g) which showed three spots on TLC. The crude product was therefore purified by flash chromatography on a column of silica gel (230–400 mesh) eluted with EtOAc which yielded as the main product 1-(4-methoxyphenyl)-6,7,8-trimethoxytetralin **16c** (228 mg, 42°). For ^1H- and ^{13}C-NMR spectra see Tables 1 and 2. *m/e* 328 (M^+, 29%), 297 (10), 292 (13), 221 (31), 215 (11), 182 (40), 181 (48), 167 (13), 151 (11), 121 (24), 110 (37). Acc. Mass M^+ 328.1674 ($C_{20}H_{24}O_4$).

Reaction of quinone-methide ketal **14a** *with TFAA.* To the crude quinone-methide ketal (1.5 g) in THF (7 ml) was added trifluoracetic anhydride (5 ml) and the mixture kept stirring at room temp for 3 hr. The resulting red soln was poured into a mixture of dichloromethane (100 ml) and water (100 ml) and the organic layer separated and washed successively with water (100 ml) and sat $NaHCO_3$ aq (2 × 100 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product (1.4 g) which showed two distinct spots on TLC in addition to some baseline material. Separation of the ether soluble material yielded two products (i) the alkene **15a** (800 mg, 55%). ν_{max}^{film} 1617, 1519, 1250, 1175 cm^{-1}. δ $CDCl_3$ 1.2–1.8m (4H), 3.70s (6H), 6.6–7.8m (10H). *m/e* 268 (M^+, 11%), 147 (100), 134 (15), 121 (65). Acc. Mass M^+ 268.1463 ($C_{18}H_{20}O_2$). (ii) Triphenylphosphine oxide (300 mg).

Reaction of quinone-methide ketal **14b** *with TFAA.* The crude quinone-methide ketal (0.66 g) in THF (4 ml) was treated with TFAA (3 ml) at room temp with stirring for 30 min. The resulting red coloured soln was poured into a 1:1 mixture of CH_2Cl_2 and water (150 ml). The organic phase was separated, washed with water (2 × 50 ml) and sat $NaHCO_3$ aq and dried ($MgSO_4$). Evaporation of the solvents *in vacuo* yielded a gummy mass (0.6 g) which showed two distinct spots by TLC in addition to a small amount of baseline material. Flash chromatography on silica gel using EtOAc as eluent gave the product (255 mg, 38%). Further examination by HPLC (Techsil 10/CH_2Cl_2) showed however that this material contained two components which were therefore separated by preparative HPLC (Lichroprep S160/CH_2Cl_2—petroleum ether gradient system). The two new components were identified as the aryltetralin **16b**, *m/e* 328 (M^+, 80%), 297 (13), 220 (13), 194 (20), 181 (75), 167 (10), 166 (17), 151 (23), 147 (13), 137 (10), 121 (25). δ $CDCl_3$ 0.7–2.1m (4H), 2.71br t (6) (2H), 3.59s (3H), 3.75s (3H), 3.83s (3H), 3.86s (3H), 3.9m (1H), 6.16s (1H), 6.80d (9) (2H), 7.00d (9) (2H), and the alkene **15b**. *m/e* 328 (M^+, 66%), 297 (11), 194 (60), 181 (71), 166 (12), 151 (46), 147 (11), 137 (13), 121 (22). δ $CDCl_3$ 1.1–1.9m (4H), 3.66, 3.69, 3.72s (12H), 6.5 7.3m (8H). Acc. Mass M^+ 328.1687 ($C_{20}H_{24}O_4$).

7-*Methoxy*-1-*tetralone* **17a**. 4-(4-Methoxyphenyl)butanoic acid (5.2 g, 27 mM) was added to polyphosphoric acid (16 g) and warmed to 90° on a steam bath. The mixture was stirred at 90° for 4 min when another portion of PPA (14 g) was added and the mixture stirred for 4 min. The mixture was then cooled to 60° and decomposed with ice and water. The resulting solid was taken up in ether, washed with water, 5% NaOH, 3% AcOH followed by 5% $NaHCO_3$ aq and dried ($MgSO_4$). On concentration of the ether soln *in vacuo* a pale yellow solid was obtained m.p. 61–62°. On crystallisation from petroleum ether (b.p. 60–80°) the product (4.5 g, 85%) had m.p. 61.5–62.5° (lit.[3] 61–62.5°). ν_{max} 1688 cm^{-1}. δ $CDCl_3$ 2.11q (6) (2H), 2.61t (6) (2H), 2.86t (6) (2H), 3.80s (3H), 6.99dd (8, 2) (1H) 7.14d (8) (1H), 7.48d (2) (1H). *m/e* 176 (M^+, 100%), 148 (27), 147 (12), 134 (18), 120 (90).

5,6,7-*Trimethoxy*-1-*tetralone* **17b**. This was prepared by cyclisation of 4-(2,3,4-trimethoxyphenyl)butanoic acid using PPA in the same way as described for the preparation of **17a**. Yield 94°. ν_{max}^{film} 1684 cm^{-1}. m.p. 76–77°. δ $CDCl_3$ 2.10q (6) (2H), 2.60t (6) (2H), 3.86s (3H), 3.89s (3H), 3.94s (3H), 7.40s (1H). Found: C, 65.74; H, 6.96. $C_{13}H_{16}O_4$ requires: C, 65.67; H, 6.77°. *m/e* 236 (M^+, 100%), 221 (24), 193 (11), 165 (14).

1-*Hydroxy*-1-(4-*methoxyphenyl*)-7-*methoxytetralin* **18a**. To Mg turnings (0.15 g, 6 mM) in THF (2 ml) was added under N_2 with stirring a soln of 4-bromomethoxybenzene (0.9 g, 5 mM) in THF (2 ml). After the addition was complete the mixture was kept stirring for 1 hr by which time most of the Mg had reacted and the soln acquired a light straw colour. This soln was then transferred using a double-ended needle to a soln of the tetralone **17a** (0.45 g, 2.5 mM) in THF (5 ml) cooled to 0°. The mixture was stirred for 4 hr at room temp and at 40° for 1.5 hr before being treated with ice and conc HCl (0.1 ml) followed by NH_4Cl aq. The organic phase was taken up in ether, washed with brine (5°) and dried ($MgSO_4$). Concentration of the soln *in vacuo* gave a gummy mass (0.72 g) which was purified by passing through a column of silica gel (flash chromatography) eluting first with CH_2Cl_2 and then ethyl acetate. The ethyl acetate fraction was concentrated to afford the product (0.41 g, 60%). ν_{max}^{film} 3500 (br), 1615, 1510, 1250, 1040 cm^{-1}. *m/e* 284 (M^+, 11%), 266 M H_2O, 100), 255 (21), 251 (29), 235 (20), 225 (20), 178 (12), 177 (14), 176 (32), 165 (11), 158 (10), 150 (14), 137 (12), 135 (49), 121 (50), 120 (10), 115 (14). δ $CDCl_3$ 1.2 2.1m (4H), 270m (2H), 3.60s (3H), 3.74s (3H), 4.00m (1H), 6.36d (3) (1H), 6.5–7.2m (6H).

1-*Hydroxy*-1-(4-*methoxyphenyl*)-5,6,7-*trimethoxytetralin* **18b**. Prepared using the same procedure as for **18a**. The crude product was purified by passing it through a short column of silica gel using ethyl acetate as eluent. Evaporation of the ethyl acetate gave the product as a gum (78%). ν_{max}^{film} 3500 (br), 1610, 1515, 1495, 1465, 1410, 1355, 1250, 1180, 1120, 1035 cm^{-1}. *m/e* 344 (M^+, 3%), 326 ($M - H_2O$, 90), 324 (11), 311 (21), 236 (31), 1.77 (22), 165 (10), 163 (11), 135 (35), 121 (15).

1-(4-*Methoxyphenyl*)-7-*methoxytetralin* **16a**. The carbinol **18a** (0.4 g) was hydrogenolysed using Pd–C (10%, 150 mg) in AcOH (50 ml) containing perchloric acid (1 ml). When no

further absorption of H_2 was observed (6 hr) the mixture was filtered and diluted with water (200 ml). Extraction with ether (2 × 100 ml) followed by washing with water (2 × 100 ml), sat $NaHCO_3$ aq (2 × 100 ml), drying ($MgSO_4$) and evaporation *in vacuo* gave a gummy mass (0.33 g, 90%). ν_{max} 1615, 1515, 1465, 1250, 1180, 1040 cm^{-1}. *m/e* 268 (M^+, 49%), 240 (14), 239 (13), 209 (15), 165 (11), 160 (100), 134 (34), 129 (10), 121 (44). The NMR spectra were identical to those of the product obtained by cyclisation of **14a** (see Tables 1 and 2). Acc. Mass M^+ 268.1463 ($C_{18}H_{20}O_2$).

1-(4-*Methoxyphenyl*)-5,6,7-*trimethoxytetralin* **16b**. Prepared by hydrogenolysis of **18b** as described for the preparation of **16a**. The product was obtained as a gum (85% yield). ν_{max}^{film} 1610, 1515, 1495, 1465, 1410, 1350, 1250, 1180, 1120, 1035 cm^{-1}. *m/e* 328 (M^+, 95%), 324 (18), 297 (16), 227 (47), 221 (29), 220 (17), 197 (18), 194 (11), 193 (11), 165 (17), 135 (20), 134 (10), 121 (51). The NMR spectra were identical to those of the product obtained by cyclisation of **14b** (see Tables 1 and 2). Acc. Mass M^+ 328.1674 ($C_{20}H_{24}O_4$).

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