Aryltricyclospirodienones; novel steroid mimics as inhibitors of aromatase

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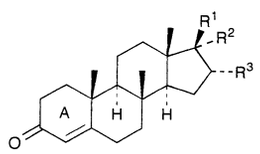
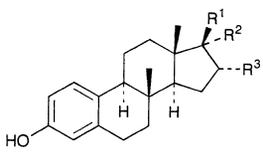
The aryltricyclospirodienones 16a, 16b, 16c and 18 have been designed as potential inhibitors of aromatase and are synthesised from 6-methoxytetralone;† compounds 16a and 18 have proved effective inhibitors with activities of the same order as aminoglutethimide.

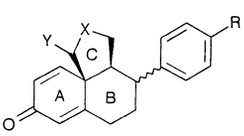
Aromatase is a key enzyme in the biogenesis of mammalian sex hormones, conducting the conversion of androgens **1a**–**c** into estrogens **2a**–**c**. The mode of action of this enzyme, which



1a R^1R^2 = O, R^3 = H
1b R^1 = OH, R^2 = R^3 = H
1c R^1 = R^3 = OH, R^2 = H



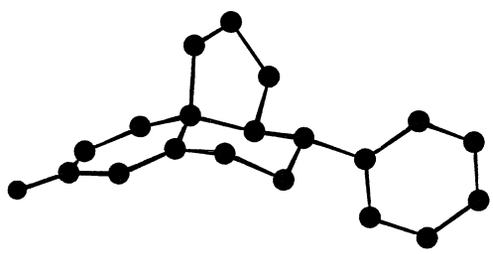
2a R^1R^2 = O, R^3 = H
2b R^1 = OH, R^2 = R^3 = H
2c R^1 = R^3 = OH, R^2 = H



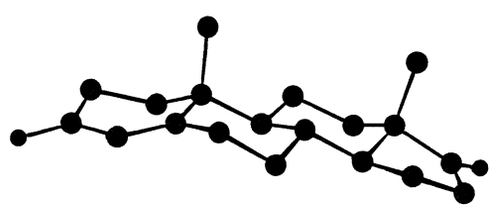
3a X = - CH_2 -
3b X = - CH_2CH_2 -

belongs to the cytochrome P-450 group, has been the subject of intense study[1] and the mechanism has been demonstrated to involve three sequential oxidative stages. The first two of these are C_{19} hydroxylations, with excision of C_{19} as formate and aromatisation as the final phase. Interest in this enzyme focuses both on sexual development in various organisms and on human diseases in which estrogens play an important role, notably certain types of carcinoma—a significant proportion of breast cancers are hormone related. In suitable circumstances reduction of estrogen levels can control such cancers and inhibition of the activity of aromatase is an attractive target enzyme for this purpose in view of its unique role. A considerable number of synthetic inhibitors have been investigated,[2a,2b] both steroidal and non-steroidal, some of which have clinical value and there is much current activity in this area. Various modes of action have been noted, including (a) reversible competitive inhibition with weak binding into the active site, (b) quasi-reversible inhibition, with strong complexation to the haem iron, (c) irreversible binding to the protein and (d) mechanism-based 'suicide' inhibition. The different types of binding can be distinguished by spectroscopic methods.

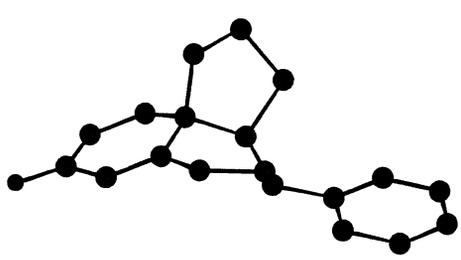
In our contribution to this field we chose to concentrate on relatives of 2-aryltetralins† as potential inhibitors. Such compounds are known to have estrogen antagonist properties[3] and frequently metabolise at a slower rate than steroidal com-



4a *trans*- Aryl 6,6,5-tricyclospirodienone



4b Androstendione



4c *cis*- Aryl 6,6,5-tricyclospirodienone

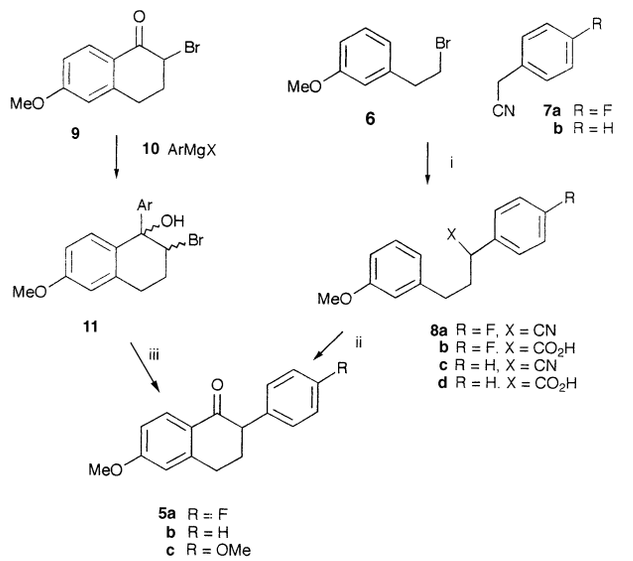
Fig. 1

pounds,[4] with clinical gain. We selected as our synthetic target the structural type **3**, containing a tricyclic spirodienone subunit, for the following reasons. In compounds of type **3** the steroid angular methyl (C_{19}) is replaced by the ring residue. The repeated oxidation at C_{19} in the steroid requires free C–Me rotation, prevented in **3**, with potential blocking of the second or third oxidation step. Also the dienone moiety echoes the androgen ring A, and the Δ^1 double bond promotes irreversible inhibition in some steroidal inhibitors.[5] Finally, we hoped that ring B would be a platform to control the spatial disposition of substituents Y in **3** close to the haem iron, thus offering possible enhancement of selectivity. Only two relative stereochemistries are feasible, those with the aryl substituent *trans* or *cis* to the bridging ring C residue. As shown in Fig. 1, the *trans* geometry **4a**[6] mimics well the natural androgen substrate geometry **4b**, allowing for the low energy barrier to rotation of the aryl substituent; interestingly the *cis* form **4c**, with a quasi-boat ring B, is also a fair match.

† IUPAC names for tetralin, tetralol and tetralone are 1,2,3,4-tetrahydronaphthalene, 1,2,3,4-tetrahydronaphthalen-1-ol and 3,4-dihydronaphthalen-1(2*H*)-one, respectively. IUPAC names are given in the Experimental section for the compounds prepared in this paper.

In some preliminary studies we explored various routes to tricyclospirodienones derived from 1-substituted tetralones.[7] In this paper we show that the desired aryl substituted analogues can be synthesised in racemic form, and that two examples display inhibitory activity comparable with that of aminoglutethimide.

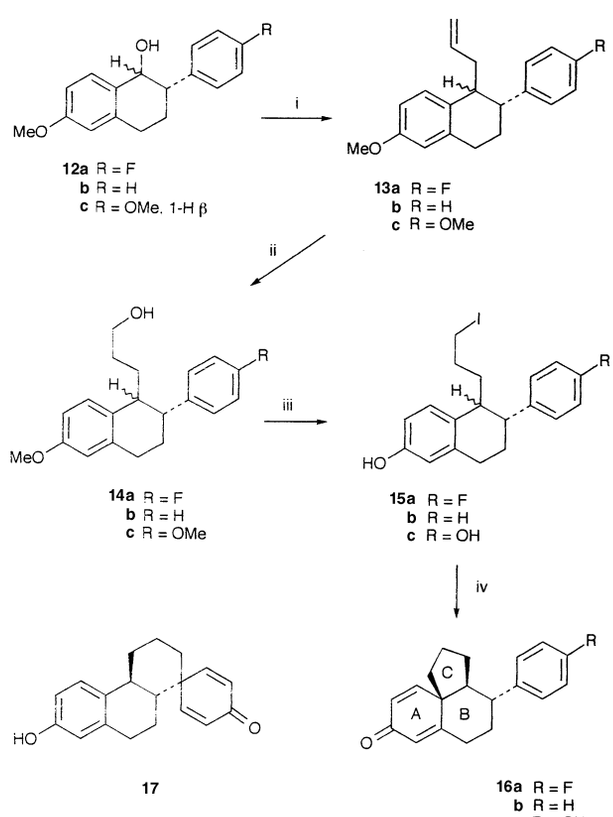
The initial requirement was a satisfactory route to 2-aryltetralones of type **5** (Scheme 1). For the fluorophenyltetralone **5a**, we adapted the route devised for 2-phenyltetralone by Campbell and Kidd.[8] Thus, 3-methoxyphenethyl bromide **6** was condensed with the 4-fluorophenylacetonitrile **7a**, using sodium sand in benzene (Scheme 1); a parallel reaction was carried out with phenylacetonitrile **7b**, to provide the nitriles **8a** (84%) and **8c** (61%) respectively. Nitrile **8a** was hydrolysed to the corresponding acid **8b** (66%) an intramolecular Friedel–Crafts cyclisation then afforded the desired 2-aryltetralone **5a** (100%); the most convenient method for this step proved to be reaction in anhydrous hydrofluoric acid at ambient temperature. Direct cyclisation of the nitrile **8a** to tetralone **5a** using Houben–Hoesch conditions proved unsatisfactory.[9]



Scheme 1 *Reagents and conditions:* i, Na, benzene, 48 h reflux; ii, MeOH, H_2SO_4, 24 h reflux; MeOH, KOH, 2 h reflux; HF, 24 h, room temp.; iii, Mg^{II}, reflux

A more direct and convenient route to **5a** was also investigated, based on the work of Hussey and Herr,[10] and Stille and Newsom.[11] This chemistry involves the addition of an aryl Grignard reagent to 2-bromotetralone; refluxing the initial product induces magnesium salt catalysed rearrangement to yield a mixture from which 2-aryltetralones can be isolated. We were able to effect selective 2-bromination (74%) of 6-methoxytetralone, using cupric bromide, and the bromide **9** was treated at 0 °C with 4-fluorophenylmagnesium bromide **10** in diethyl ether. The reaction mixture was then refluxed for 2 h and column chromatography of the product led to the isolation of 2-(4-fluorophenyl)-6-methoxytetralone **5a**, albeit in only 15% yield. The corresponding 2-phenyl compound **5b** was similarly prepared in 13% yield. The reaction proceeds through the *cis* and *trans* halohydrins **11**.[11] Although these are poor yields, they compare favourably with the overall return from the stepwise procedure and are much more direct.

The route adopted to the target spirodienones is outlined in Scheme 2. Reduction of the tetralones **5a–c** gave the corresponding tetralols **12a–c**; using sodium borohydride, mixtures (*ca.* 2:1) of the *cis* and *trans* aryl alcohols were obtained. Stereoselectivity could be achieved with other reagents; thus, reduction of *e.g.* 2-(4-methoxyphenyl)-6-methoxytetralone **5c**,[12] with L-Selectride at 0 °C afforded exclusively the *cis* tetralol **12c**.† The methodology for introducing functionalised alkyl chains at C-1 in tetralins is limited, but we have found that an allyl group can be efficiently inserted by reaction of a 1-tetralol with allyl trimethylsilane–zinc iodide. Using these reagents, tetralols **12a–c** were converted into the 1-allyl derivatives **13a–c** in good yield. However the *cis* tetralol **12c** gave a mixture of two geometric isomers (*ca.* 2:1) and we were unable to find reaction conditions under which the reaction proceeded stereoselectively. Disappointingly we did not discover a way to separate the diastereoisomers of the allyl compounds **13a–c** using HPLC. We therefore continued to tolerate diastereoisomeric mixtures in the sequence, hoping to effect separation or selective reaction at a later stage. Hydroboration–oxidation afforded the corresponding primary alcohols **14a–c**. Treatment with trimethylsilyl chloride–sodium iodide in acetonitrile then provided the phenolic iodides **15a–c**, *via* concurrent demethylation and hydroxy substitution. Finally the phenolic iodides, as (2:1) diastereoisomeric mixtures, were refluxed with potassium *tert*-butoxide in *tert*-butyl alcohol to afford the desired aryl tricyclospirodienones **16a–c**. These were obtained in low yield (10–15%), possibly since the spirocyclisations were sluggish (24 h reflux required) and other reactions competed, *e.g.* elimination. However in compensation the final products **16a–c** were obtained as single diastereoisomers, as shown unequivocally by ^{13}C NMR spectroscopy. It seems likely that the compounds have the aryl substituent *trans* to bridging ring C. In support, MM2 calculations[6] show that for **16a** the *trans* geometry is substantially more stable (*ca.* 15 kJ mol^{-1}) than the *cis* isomer, while the *trans* iodide **15a** is only *ca.* 6 kJ mol^{-1} more stable than its *cis* counterpart. Since a product-like transition state is to be expected, the *trans* iodide **15a** would have a lower activation energy for spirocyclisation than the *cis* form and the *trans* system should cyclise significantly faster. Given the slow cyclisation rate and loss of material in side reactions, it is not surprising that only one diastereoisomer could be detected, almost certainly then the *trans* compounds **16** as shown. It should be said that at

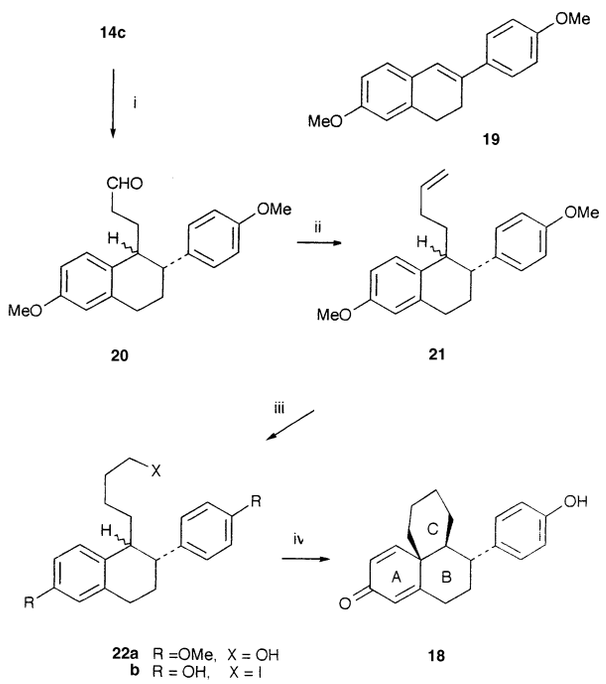


Scheme 2 *Reagents and conditions:* i, $Me_3SiCH_2CH{=}CH_2$, ZnI_2; ii, BH_3Me_2S; NaOH, H_2O_2; iii, Me_3SiCl, NaI, MeCN; iv, Bu^tOK, Bu^tOH, 24 h, reflux

present no spectroscopic evidence can be advanced to substantiate the stereochemical conclusions, the ^{1}H NMR spectra at 400 MHz being too complex to elucidate.

The iodide **15c** has two possible pathways for spirocyclisation, leading either to **16c** or to the isomer **17**. The ^{13}C NMR data for the product show clear parallels with those for **16a** and **16b** and support the assignment as **16c**.

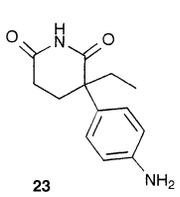
We also set out to synthesise a further member of this group of tricyclospirodienone, **18**, with a 6,6,6-ABC ring system. Our initial plan involved addition of a C_4 side chain to a tetralol pivaloate, as in development work.[7] Such an approach was frustrated by the facile accompanying elimination reaction to the



Scheme 3 *Reagents and conditions:* i, PCC, CH_2Cl_2, room temp.; ii, $Ph_3P{=}CH_2$, THF, −78 °C; iii, BH_3–Me_2S; NaOH, H_2O_2; Me_3SiCl, NaI, MeCN; iv, Bu^{t}OK, Bu^{t}OH, reflux 24 h

stilbene-like product **19** and we were forced to employ a more circuitous route *via* alcohol **14c**. Thus standard oxidation to the aldehyde **20** followed by Wittig reaction to form alkene **21**, enabled hydroboration to the homologated alcohol **22a**. Demethylation–iodination afforded **22b**, which cyclised to yield the desired spirodienone **18**; NMR data indicate that the phenolic ring D is still intact.

The compounds described above were then tested *in vivo* for anti-aromatase activity using human term placental microsomes.[13] Aminoglutethimide **23**,[14] an inhibitor which has been



used in the clinic, was tested at the same time. The table shows the activity of a selected few compounds including aminoglutethimide, under parallel conditions, expressed as percentage inhibition.

It can be seen that three of the tricyclospirodienones are effective inhibitors, and that two, compounds **16a** and **18**, display activities comparable to that of aminoglutethimide. The dienone with the lowest activity of the three, **16b**, lacks a polar function in ring D; the latter mimicks the ring D oxygen functions of the androgens, and is likely to be a requirement for activity. These results are extremely encouraging and suggest that further work in this area would be rewarding, especially since all the new compounds were tested as racemates. The synthesis of homochiral samples, and compounds functionalised in ring C are the clear future targets.

Table 1 Inhibition of aromatase by various compounds

Compound	% Inhibition
Aminoglutethimide **23**	85
Tricyclospirodienone **16b**	20
Tricyclospirodienone **16a**	86
Tricyclospirodienone **18**	77

Experimental

General details

Unless otherwise stated the following apply. Melting points were recorded using a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured in deuteriochloroform using internal TMS standard; multiplicities in ^{13}C NMR were obtained using a DEPT sequence. Mass spectra were obtained using electron impact or chemical ionisation. Infrared spectra were collected from thin films (oils) or potassium bromide discs (solids). All solvents were dried by standard methods before use; 'light petroleum' was the fraction bp 40–50 °C. 'Evaporation' refers to evaporation under reduced pressure; 'washed' indicates the use of water and aqueous sodium hydrogen carbonate as appropriate; 'dried' implies the use of magnesium sulfate. 'Chromatography' means column chromatography using silica gel 60; eluting solvents are listed.

2-Bromo-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one 9

6-Methoxy-1-tetralone (10 g, 0.057 mol) in chloroform (70 ml) was added slowly to a refluxing stirred suspension of cupric bromide (22.5 g, 0.1 mol) in ethyl acetate (75 ml), and the mixture was refluxed for 2 h. The mixture was filtered, washed with water and aq. sodium hydrogen carbonate, dried and evaporated. The residual solid was crystallised from light petroleum (bp 60–80 °C)–dichloromethane to yield the title bromo ketone (9.45 g, 74%), mp 80–81 °C (lit.,[15] mp 83 °C) (Found: C, 51.91; H, 4.26; Br, 31.23%; *m*/*z* 253.992. $C_{11}H_{11}BrO_2$ requires C, 51.79; H, 4.35; Br, 31.32%; M^+, 253.994).

2-(4-Fluorophenyl)-4-(3-methoxyphenyl)butanonitrile 8a

4-Fluorophenylacetonitrile (2.51 g, 18.6 mmol) was added to sodium sand (0.43 g, 18.6 mmol) under dry diethyl ether (30 ml). This mixture was stirred under reflux (nitrogen) for 2 h and then cooled to 0 °C when 3-methoxyphenethyl bromide (2.0 g, 9.3 mmol) was added. The reaction mixture was stirred overnight when the diethyl ether was evaporated and replaced with benzene (50 ml). The resulting suspension was refluxed for 48 h, cooled and quenched with dil. hydrochloric acid. The organic layer was washed, dried and evaporated and the residue was chromatographed to afford the *title nitrile* (2.11 g, 84%) (Found: *m*/*z* 269.124. $C_{17}H_{16}NFO$ requires M^+, 269.122); ν_{max}/cm^{-1} 2241; δ_H 2.05–2.32 (2 H, m, 3-CH_2), 2.77 (2 H, t, *J* 6.3, 4-CH_2), 3.72 (1 H, t, *J* 6.3, 2-CH), 3.80 (3 H, s, OCH_3), 6.76 (3 H, m, 3 × CH), 7.06 (2 H, m, 2 × CH), 7.20–7.32 (3 H, m, 3 × CH).

2-(4-Fluorophenyl)-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one 5a

The nitrile **8a** was hydrolysed with 10% methanolic sulfuric acid at reflux for 24 h. Standard isolation procedures afforded 2-(4-*fluorophenyl*)-4-(3-*methoxyphenyl*)*butanoic acid* (66%), mp 101–103 °C (Found: C, 71.00; H, 5.98%; *m*/*z* 288.117. $C_{17}H_{17}FO_3$ requires C, 70.82; H, 5.94%; M^+, 288.116);

ν_{max}/cm^{-1} 3700–2400, 1708. This acid (250 mg, 0.87 mmol) was dissolved in anhydrous hydrofluoric acid (4.5 g) and the solution was set aside overnight. The hydrofluoric acid was then evaporated and the residue was dissolved in diethyl ether–dichloromethane (2:3); this solution was then washed (aq. sodium hydroxide), dried and evaporated. The residue was chromatographed to yield the *title ketone* (200 mg, 80%), mp 133–134 °C (Found: C, 75.39; H, 5.71%; *m*/*z* 270.170. $C_{17}H_{15}FO_2$ requires C, 75.54; H, 5.59%; M^+, 270.106); ν_{max}/cm^{-1} 1672; δ_H 2.3–2.4 (2 H, m, 3-CH_2), 2.9–3.2 (2 H, m, 4-CH_2), 3.74 (1 H, dd, *J* 8, 8, 2-CH), 3.87 (3 H, s, OCH_3), 6.72 (1 H, d, *J* 2.6, 5-CH), 6.85 (1 H, dd, *J* 8.7, 2.6, 7-CH), 7.02 (2 H, m, 2 × CH), 7.14 (2 H, m, 2 × CH), 8.06 (1 H, d, *J* 8.7, 8-CH); δ_C 29.15 (3-CH_2), 31.39 (4-CH_2), 53.37 (2-CH), 55.47 (OCH_3), 112.54, 113.35 (5-CH, 7-CH), 115.30 (2 × CH, d, $^2J_{CF}$ 20.7, 3′-CH, 5′-CH), 126.31 (4a-C), 129.94 (2 × CH, d, $^3J_{CF}$ 7.4, 2′-CH, 6′-CH), 130.29 (8-CH), 135.73 (1′-C, d, J_{CF} 3.6), 146.47 (8a-C), 161.76 (4′-C, d, $^1J_{CF}$ 244.1), 163.68 (6-C), 196.74 (C=O).

Reaction of 2-bromo-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one 9 with aryl Grignard reagents

(a) 4-Fluorophenylmagnesium bromide (2 M in diethyl ether, 15.2 ml) was added dropwise to a solution of 2-bromo-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one **9** (7.58 g, 30 mmol) in toluene (40 ml) at 0 °C and the solution was allowed to warm to ambient temperature before refluxing for 2 h. The reaction mixture was quenched with aq. ammonium chloride and the organic layer was washed, dried and evaporated. The residue was chromatographed [dichloromethane–light petroleum (3:1)] to yield 2-(4-*fluorophenyl*)-6-*methoxy*-3,4-*dihydronaphthalen*-2(1*H*)-*one* **5a** (1.2 g, 15%), indistinguishable from the above sample.

(b) In parallel fashion, phenylmagnesium bromide was employed to provide 2-phenyl-6-methoxy-3,4-dihydronaphthalen-2(1*H*)-one **5b** (13%), mp 118–119 °C (lit.,[16] mp 113–116 °C (Found: C, 81.2; H, 6.44%; *m*/*z* 252.112. $C_{17}H_{16}O_2$ requires C, 80.93; H, 6.39%; M^+, 252.115).

2-Aryl-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ols 12

(a) L-Selectride (10.2 ml, 1.0 M in THF) was diluted with THF (20 ml) and the solution was cooled to 0 °C, when (4-methoxyphenyl)-6-methoxy-1-tetralone[12] (2.82 g, 0.1 mol) in THF was added over 5 min. The reaction mixture was stirred for 4 h when aq. sodium hydroxide (15 ml, 4 M) and aqueous hydrogen peroxide (5 ml, 30%) were added. Stirring was continued overnight when the mixture was diluted with water (150 ml) and extracted with diethyl ether. The organic extracts were washed, dried and evaporated, and the residue was chromatographed (30% diethyl ether–light petroleum) to yield cis-2-(4-*methoxyphenyl*)-6-*methoxy*-1,2,3,4-*tetrahydronaphthalen*-1-*ol* **12c** (1.78 g, 63%) as a single diastereoisomer, mp 103–104 °C (Found: C, 76.27; H, 7.23%; *m*/*z* 284.147. $C_{18}H_{20}O_3$ requires C, 76.03; H, 7.09%; M^+, 284.141); ν_{max}(KBr)/cm^{-1} 3422 (br); δ_H 1.63 (1 H, br s, OH), 1.86 (1 H, m, 3-CH_{ax}), 2.36 (1 H, m, J_{gem} 12.8, 3-CH_{eq}), 2.78–3.00 (2 H, m, 4-CH_2), 3.00 (1 H, ddd, *J* 10.0, 2.8, 2.8, 2-CH), 3.77 and 3.79 (each 3 H, s, OCH_3), 4.62 (1 H, d, *J* 2.8, 1-CH), 6.67 (1 H, d, *J* 2.6, 5-CH), 6.75 (1 H, dd, *J* 2.6, 8.4, 7-CH), 6.90 (2 H, d, *J* 8.8, 2 × 11-CH), 7.23 (1 H, d, *J* 8.4, 8-CH) and 7.23 (2 H, d, *J* 8.8, 2 × 10-CH). Reduction with sodium borohydride in methanol gave a 2:1 mixture of the *cis* and *trans* diastereoisomers.

(b) 2-Phenyl-6-methoxy-3,4-dihydronaphthalen-2(1*H*)-one **5b** (0.3 g, 1.2 mmol) was dissolved in methanol (20 ml) with sodium borohydride (0.1 g, 2.63 mmol). After 2 h at ambient temperature the reaction mixture was poured into water and the product was isolated *via* diethyl ether extraction and purified by column chromatography (1% methanol–dichloromethane) to yield 2-*phenyl*-6-*methoxy*-1,2,3,4-*tetrahydronaphthalen*-1-*ol* **12b** (0.23 g, 76%) as a 2:1 mixture of *cis* and *trans* isomers (Found: *m*/*z* 254.132. $C_{17}H_{18}O_2$ requires M^+, 254.130); ν_{max}(film)/cm^{-1} 3414 (br).

(c) 2-(4-Fluorophenyl)-6-methoxy-3,4-dihydronaphthalen-1(2*H*)-one **5a** (1.65 g, 6.11 mmol) was treated with sodium borohydride as in the preceding experiment, to afford 2-(4-*fluorophenyl*)-6-*methoxy*-1,2,3,4-*tetrahydronaphthalen*-1-*ol* **12a** (1.48 g, 89%) as a 2:1 mixture of *cis* and *trans* isomers (Found: *m*/*z* 272.120 $C_{17}H_{17}FO_2$ requires M^+, 272.12); ν_{max}(KBr)/cm^{-1} 3415 (br); δ_H 1.85–2.15 (2 H, m, 3-CH_2), 2.8–3.1 (3 H, br m, 4-CH_2, 2-CH), 3.81 (3 H, s, OCH_3), 4.71 (d, *J* 2.6, 1-CH, *cis* isomer), 4.76 (d, *J* 9.0, 1-CH, *trans* isomer), 6.65 (m), 6.8 (m) and 7.25 (m) (total 7 H, ArH).

1-Allyl-2-aryl-6-methoxy-1,2,3,4-tetrahydronaphthalenes 13

(a) *cis*-2-(4-Methoxyphenyl)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol **12c** (1.42 g, 5.0 mmol) in dichloromethane (5 ml) was added dropwise to a mixture of allyltrimethylsilane (2.85 g, 25 mmol) and boron trifluoride–diethyl etherate (0.75 g, 5.3 mmol) in dichloromethane (10 ml) under nitrogen at −78 °C. The mixture was stirred for 3 h and then quenched with aq. sodium hydrogen carbonate. The organic phase was separated, washed, dried and evaporated, and the residue was chromatographed (10% diethyl ether–light petroleum) to yield 1-*allyl*-2-(4-*methoxyphenyl*)-6-*methoxy*-1,2,3,4-*tetrahydronaphthalene* **13c** (1.10 g, 72%) as a mixture of diastereoisomers (*ca.* 3:1). HPLC (reversed phase) gave a sample of the major isomer (Found: *m*/*z* 208.180. $C_{21}H_{24}O_2$ requires M^+, 308.178); δ_H 1.95–2.05 (4 H, m, 3-CH_2, CH_2=CHCH_2), 2.95 (3 H, m, 2-CH, 4-CH_2), 3.20 (1 H, dt, *J* 12.2, 3.9, 1-CH), 3.77 and 3.78 (each 3 H, s, OCH_3), 4.72 (1 H, d, *J* 17.2, CH_2=CH, *trans*), 4.82 (1 H, d, *J* 10.2, CH_2=CH, *cis*), 5.56 (1 H, m, CH_2=C*H*), 6.65 (2 H, m, 5-CH, 7-CH), 6.86 (2 H, d, *J* 8.6, 2 × 11-CH), 7.01 (1 H, d, *J* 9.2, 8-CH), 7.12 (2 H, d, *J* 8.6, 2 × 10-CH); δ_C 23.18 (3-CH_2), 29.47 (4-CH_2), 36.12 (CH_2=CH*C*H_2), 42.77, 43.95 (1-CH, 2-CH), 55.13, 55.20 (OCH_3), 111.21, 113.42, 113.53 (5-CH, 7-CH, 11-CH), 115.51 (*C*H_2=CH), 128.82 (10-CH), 130.46 (8-CH), 132.79, 136.46, 137.12 (4a-C, 8a-C, 9-C), 138.08 (CH_2=*C*H), 157.75, 157.86 (6-C, 12-C).

(b) 2-(4-Fluorophenyl)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol **12a** (0.36 g, 1.32 mmol) in dichloromethane (10 ml) at 0 °C was treated with allyltrimethylsilane (0.18 g, 1.6 mmol) and zinc iodide (0.51 g, 1.6 mmol) for 30 min. Isolation of the product as in the above experiment provided 1-*allyl*-2-(4-*fluorophenyl*)-6-*methoxy*-1,2,3,4-*tetrahydronaphthalene* **13a** (0.332 g, 85%) as a mixture of diastereoisomers (*ca.* 2:1) (Found: *m*/*z* 296.160. $C_{20}H_{21}FO$ requires M^+, 296.158); δ_H 1.8–2.3 and 2.5–3.3 (total 8 H), 3.794 and 3.796 (total 3 H, OCH_3), 4.7 (1 H, br d, *J* 18.4, CH_2=CH, *trans*), 4.8 (1 H, d, *J* 10, CH_2=CH, *cis*), 5.55 (1 H, m, CH_2=C*H*), 6.6–6.8 and 6.9–7.2 (total 7 H, ArH).

(c) In an experiment parallel to (b) above, 2-phenyl-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-ol **12b** was reacted with allyltrimethylsilane to yield 1-*allyl*-2-*phenyl*-6-*methoxy*-1,2,3,4-*tetrahydronaphthalene* **13b** (78%) as a mixture of diastereoisomers (*ca.* 2:1) (Found: *m*/*z* 278.164. $C_{20}H_{22}O$ requires M^+, 278.167).

2-Aryl-1-(3-hydroxypropyl)-6-methoxy-1,2,3,4-tetrahydronaphthalenes 14

(a) 1-Allyl-2-(4-methoxyphenyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene **13c** (0.311 g, 1.01 mmol) in THF at 0 °C was treated with borane–dimethyl sulfide complex (1 M, 0.108 ml). The solution was then stirred at ambient temperature for 3 h before refluxing for 1 h. The cooled mixture was diluted with ethanol and aq. sodium hydroxide (2 M, 0.7 ml) and hydrogen peroxide (30%, 0.12 ml) were added. After refluxing the mixture for 1 h, it was poured into water and extracted with diethyl ether. The organic extracts were washed, dried and evaporated. The residue was chromatographed (70% diethyl ether–light petroleum) to afford 1-(3-*hydroxypropyl*)-2-(4-*methoxyphenyl*)-6-*methoxy*-1,2,3,4-*tetrahydronaphthalene* **14c** (1.151 g, 46%) (Found: *m*/*z* 326.188. $C_{21}H_{26}O_3$ requires M^+, 326.188); δ_C(major diastereo-

isomer) 22.75, 27.03, 29.09, 31.29 (4 × CH_2), 42.63, 43.59 (1-CH, 2-CH), 55.06 (2 × OCH_3), 63.00 (CH_2OH), 111.14, 113.44, 113.55 (5-CH, 7-CH, 11-CH), 128.64 (10-CH), 130.03 (8-CH), 133.60, 136.41, 136.93 (4a-C, 8a-C, 9-C), 157.11 and 157.68 (6-C, 12-C).

(b) In parallel experiments, 1-allyl-2-(4-fluorophenyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene **13a** and 1-allyl-2-phenyl-6-methoxy-1,2,3,4-tetrahydronaphthalene **13b** yielded, respectively, 2-(4-*fluorophenyl*)-1-(3-*hydroxypropyl*)-6-*methoxy*-1,2,3,4-*tetrahydronaphthalene* **14a** (59%) (Found: *m*/*z* 314.71. $C_{20}H_{23}FO_2$ requires M^+, 314.168) and 1-(3-*hydroxypropyl*)-6-*methoxy*-2-*phenyl*-1,2,3,4-*tetrahydronaphthalene* **14b** (34%) (Found: *m*/*z* 296.180. $C_{20}H_{40}O_2$ requires M^+, 296.178), both as (2:1) mixtures of diastereoisomers.

1-(But-3-enyl)-2-(4-methoxyphenyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene 21

1-(3-Hydroxypropyl)-2-(4-methoxyphenyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene **14c** (0.3 g, 0.9 mmol) in dichloromethane (2 ml) was added to a stirred suspension of pyridinium chlorochromate (0.3 g, 1.35 mmol) in dichloromethane (2 ml). After 2 h diethyl ether (10 ml) was added. The supernatant, with diethyl ether washings from the residue, was passed through a kieselguhr pad and evaporated; column chromatography (2:1 light petroleum–diethyl ether) gave the *aldehyde* **20** (0.22 g, 70%) as a (2:1) mixture of diastereoisomers (Found: *m*/*z* 324.173. $C_{21}H_{24}O_3$ requires M^+, 324.173); ν_{max}/cm^{-1} 1723; δ_H 1.5–2.4 and 2.7–3.3 (total 10 H), 3.786, 3.791, 3.793 and 3.810 (total 6 H, all s, OCH_3), 6.6–7.2 (7 H, ArH), 9.50 and 9.65 (total 1 H, both t, *J* 2, CHO). The aldehyde (0.25 g) was added to methylene(triphenyl)phosphorane [from methyltriphenylphosphonium iodide (0.47 g, 1.16 mmol) and butyllithium (1.28 mmol)] in THF (10 ml) at −78 °C. The reaction mixture was allowed to warm to ambient temperature over 60 min, when water (10 ml) was added and the mixture was extracted with diethyl ether. The extracts were washed, dried and evaporated. The residue was chromatographed (9:1 light petroleum–diethyl ether) to afford the *title but*-3-*enyltetralin* **21** (0.144 g, 58%) also as a (2:1) mixture of diastereoisomers (Found: *m*/*z* 322.191. $C_{22}H_{26}O_2$ requires M^+, 322.193); δ_H 1.5–2.2 and 2.5–3.1 (total 10 H), 3.781, 3.789, 3.795 and 3.803 (total 6 H, all s, OCH_3), 4.8–5.0 (2 H, m, CH=CH_2), 5.5–5.8 (1 H, m, C*H*=CH_2), 6.6–6.9 and 7.0–7.2 (total 7 H, ArH).

1-(4-Hydroxybutyl)-2-(4-methoxyphenyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene 22a

Borane–dimethyl sulfide (2 M, 0.35 ml) was added dropwise to 1-(but-3-enyl)-2-(4-methoxyphenyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene **21** (0.4 g, 1.24 mmol) in hexane (20 ml) at 0 °C. After 3.5 h at ambient temperature the solution was refluxed for 1.5 h. Ethanol (10 ml), aq. sodium hydroxide (2 M, 5 ml) and hydrogen peroxide (30%, 0.25 ml) were added sequentially to the cooled (0 °C) mixture, which was then refluxed for 1 h when it was cooled, diluted with water and extracted with dichloromethane. The extracts were washed, dried and evaporated to leave a residue which was chromatographed (1:2 light petroleum–diethyl ether) to afford the *title alcohol* **22a** (0.319 g, 76%) as a (2:1) mixture of diastereoisomers (Found: *m*/*z* 340.025. $C_{22}H_{28}O_3$ requires M^+, 340.204); ν_{max}(film)/cm^{-1} 3377 (br).

Aryltricyclospirodienones 16 and 18

(a) A mixture of 1-(3-hydroxypropyl)-2-(4-methoxyphenyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene **14c** (0.122 g, 0.375 mmol), sodium iodide (0.31 g, 2.1 mmol), chlorotrimethylsilane (0.2 g, 1.8 mmol) and acetonitrile (10 ml) were heated together under reflux overnight (nitrogen) and then poured into ice–water (50 ml). The product mixture was extracted with diethyl ether and the extracts were washed, dried and evaporated. The residue was purified by chromatography (1:1 light petroleum–diethyl ether) to provide the *phenolic iodide* **15c** (0.1 g, 65%) (Found: *m*/*z* 408.060. $C_{19}H_{21}IO_2$ requires M^+, 408.059). This iodide (68.6 mg, 0.168 mmol) was dissolved in *tert*-butyl alcohol (17 ml) with potassium *tert*-butoxide (22 mg, 0.196 mmol) and the solution was refluxed (nitrogen) overnight. The reaction mixture was then diluted with water (50 ml) and extracted with ethyl acetate. The organic extracts were dried and evaporated and the residue (39 mg) was extracted with *N*,*N*-dimethylformamide to yield (3a*R**,4*R**,10a*S**)-4-*phenyl*-1,2,3,3a,4,5,-6,8-*octahydrocyclopenta*[d]*naphthalen*-8-*one* **16c** as a single diastereoisomer with low solubility in common organic solvents (Found: *m*/*z* 280.148. $C_{19}H_{20}O_2$ requires M^+, 280.146); ν_{max}(KBr)/cm^{-1} 1652, 1609, 1516; δ_H([$^2H_7$]DMF) 1.5–3.0 (12 H, m, 2 × CH, 5 × CH_2), 6.04 (1 H, dd, *J* 1.9, 9.8, 3-CH), 6.13 (1 H, d, *J* 1.9, 1-CH), 6.78 (2 H, d, *J* 8.3, 3′-CH, 5′-CH), 7.05 (2 H, d, *J* 8.3, 2′-CH, 6′-CH), 7.11 (1 H, d, *J* 9.8, 4-CH), 9.38 (1 H, s, OH); δ_C([$^2H_7$]DMF) 22.82, 26.43, 28.57, 29.08 (7-CH_2, 9-CH_2, 10-CH_2, 11-CH_2), 39.92 (8-CH_2), 40.92 (6-CH), 51.75 (4a-C), 53.36 (5-CH), 115.67 (3′-CH, 5′-CH), 125.01, 127.47 (1-CH, 3-CH), 129.01 (2′-CH, 6′-CH), 134.47 (1′-C), 156.87 (4′-C), 157.27 (4-CH), 167.15 (8a-C), 186.13 (C=O).

(b) 2-(4-Fluorophenyl)-1-(3-hydroxypropyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene **14a** (0.69 g, 2.2 mmol) was refluxed in acetonitrile (40 ml) with sodium iodide (1.8 g, 12.1 mmol) and chlorotrimethylsilane (1.21 g, 11.0 mmol) for 24 h. The mixture was diluted with water (40 ml) and extracted with diethyl ether. The extracts were washed, dried, evaporated and the residue was purified by chromatography (2:1 light petroleum–diethyl ether) to yield the *iodide* **15a** (0.624 g, 67%) (Found: *m*/*z* 410.052. $C_{19}H_{20}FIO$ requires M^+, 410.054). This iodide (0.1 g, 0.246 mmol) was dissolved in *tert*-butyl alcohol (10 ml) with potassium *tert*-butoxide (34 mg, 0.3 mmol) and the solution was heated at reflux for 48 h, after which it was poured into water (25 ml). The product mixture was extracted with dichloromethane and the extracts were washed, dried and evaporated; the residue was purified by chromatography (1:1 to 1:2 light petroleum–diethyl ether) to afford (3a*R**,4*R**,10a*S**)-4-(4-*fluorophenyl*)-1,2,3,3a,4,5,6,8-*octahydronaphthalen*-8-*one* **16a** as a single diastereoisomer (10.6 mg, 15%) (Found: *m*/*z* 282.142. $C_{19}H_{18}FO$ requires M^+, 282.142); ν_{max}(KBr)/cm^{-1} 1659, 1621, 1601; δ_C 21.4, 28.5, 33.1, 35.6, 36.7 (5 × CH_2), 45.5 (CH), 52.0 (C), 54.0 (CH), 115.4 (3′-CH, 5′-CH, d, $^2J_{CF}$ 20.8), 126.3, 126.6 (2 × CH), 129.2 (2′-CH, 6′-CH, d, $^3J_{CF}$ 7.4), 139.5 (C), 153.4 (CH), 161.5 (C, d, $^1J_{CF}$ 250), 165 (C), 187 (C=O).

(c) 1-(3-Hydroxypropyl)-2-phenyl-6-methoxy-1,2,3,4-tetrahydronaphthalene **14b** (80 mg, 0.27 mmol) was treated with chlorotrimethylsilane (200 mg, 1.8 mmol) and sodium iodide (310 mg, 2.1 mmol) in acetonitrile (5 ml) as in the preceding experiment: isolation and purification of the product in similar fashion gave the *iodide* **15b** (40 mg, 38%) [Found: *m*/*z* 264.152. $C_{19}H_{21}IO$ requires (M^+ − HI), 264.151]. Cyclisation of this iodide (28 mg, 0.07 mmol) with potassium *tert*-butoxide (10 mg, 0.09 mmol) in *tert*-butanol (10 ml) as described above afforded (3a*R**,4*R**,10a*S**)-4-*phenyl*-1,2,3,3a,4,5,6,8-*octahydronaphthalen*-8-*one* **16b** as a single diastereoisomer (2 mg, 10%) (Found: *m*/*z* 264.149. $C_{19}H_{20}O$ requires M^+, 264.151); ν_{max}(KBr)/cm^{-1} 1657; δ_H 1.5–2.7 (12 H), 6.15–6.3 (2 H, br m, 1-CH, 3-CH), 6.9–7.35 (6 H, 4-CH, PhH).

(d) Using the above protocol for iodination–demethylation, 1-(4-hydroxybutyl)-2-(4-methoxyphenyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene **22a** (0.25 g, 0.74 mmol) was treated with chlorotrimethylsilane (0.44 g, 4.05 mmol) to yield after chromatography (4:1 to 1:1 light petroleum–diethyl ether) the *phenolic iodide* **22b** (0.105 g, 34%) (Found: *m*/*z* 422.074. $C_{20}H_{23}IO_2$ requires M^+, 422.074). Monodemethylated material was also isolated. The phenolic iodide **22b** (75 mg) was cyclised with potassium *tert*-butoxide as in the preceding experiments. Product isolation as before and chromatography (3:1 to 1:1 light petroleum–ethyl acetate) afforded (4a*R**,5*R**,11a*S**)-5-(4-*hydroxyphenyl*)-2,3,4,4a,5,6,7,9-*octahydro*-1H-*benzo*[d]*naphthalen*-

9-*one* **18** as a single diastereoisomer (3.4 mg, 6.5%) (Found: *m*/*z* 294.161. $C_{20}H_{22}O_2$ requires M^+, 294.162; ν_{max}(KBr)/cm^{-1} 3435 (br), 1655, 1613, 1515; δ_H 0.7–3.2 (14 H), 6.17 (1 H, br d, *J* 2.0, 1-CH), 6.33 (1 H, dd, *J* 10.4, 2.0, 3-CH), 6.77 (2 H, d, *J* 8.6, 2′-CH, 6′-CH), 7.01 (2 H, d, *J* 8.6, 3′-CH, 5′-CH), 7.64 (1 H, d, *J* 10.4, 4-CH).

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