Applications of the spiroannulation of tetralins with alkynes; towards new anti-estrogenic compounds

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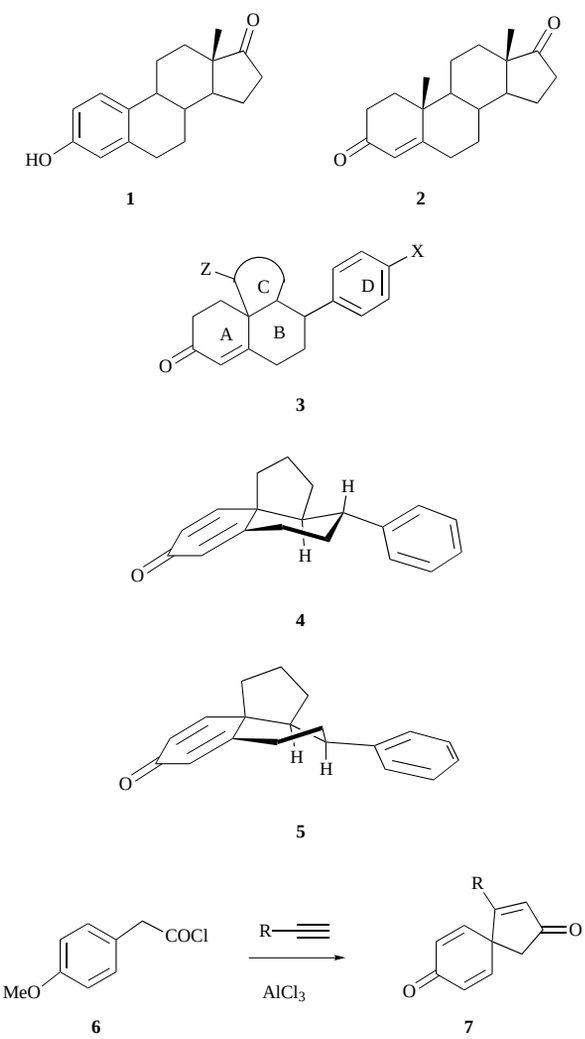
Thermal reaction of the benzocyclobutene 17 with 4-methoxystyrene leads to 1-cyano-2-(4-methoxyphenyl)-6-methoxytetralin† 19 through an electrocyclic ring opening Diels–Alder sequence: the derived acid chloride 20, and its analogue 10, then undergoes an unusual addition–cyclisation reaction with alkynes catalysed by aluminium chloride, to yield the tricyclospirodienones 21a–c and 11a,b; the former set show moderate aromatase inhibitory activity.

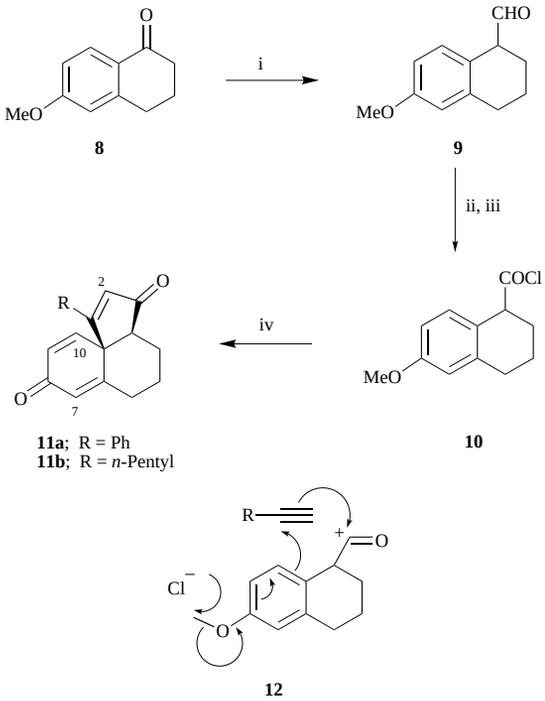
Estrogenic hormones *e.g.* estrone **1** are formed in human metabolism from the primary steroid cholesterol *via* androgens *e.g.* androstendione **2**, in a predominantly oxidative sequence. Formation of **1** from **2** is catalysed by a single cytochrome P-450 enzyme, aromatase, which effects oxidation of C-19 to formyl level before scission of the C-10–C-19 bond and aromatisation.[1]

Control of estrogen levels is of considerable importance in the treatment of steroid hormone induced diseases such as mammary carcinoma and drugs used clinically for such conditions, *e.g.* aminoglutethimide, exploit inhibition of aromatase for these ends. As we have expounded in detail in previous papers on this topic,[2] there is considerable interest in designing new inhibitors with improved selectivity towards the aromatase P-450 system. For reasons which we have also elaborated before[2a] we opted to develop systems such as **3**, based on a 2-aryldecalin modified with a bridged ring which replaces the steroid C-19 and could provide both a barrier to complete enzymic oxidation and a relatively rigid platform for functionality. Molecular modelling[2a] indicates that both *trans*- and *cis*-aryltricyclospirodienones **4** and **5**, with aryl groups pseudo equatorial in both cases (in half chair and half boat cyclohexenes respectively), correspond well to the androstendione framework, and might be expected to be biologically active, albeit to different degrees. Recently we have reported our synthetic work with *trans*-aryltricyclospirodienones,[2a] and demonstrated that some examples inhibit aromatase *in vitro* with a similar order of activity to aminoglutethimide. In this paper we outline a novel approach to the synthesis of tricyclospirodienones and apply the method to compounds of the *cis* series; these results have figured in a preliminary publication.[2e]

In this work we took a lead from an observation of Haack and Beck,[3] who found that attempted acylation of certain alkynes by 4-methoxyphenylacetyl chloride **6** afforded the spirocyclohexadienones of type **7**: we confirmed this observation by successfully forming spirodienone **7**; R = Bu by their method. This appeared an attractive prospect for a rapid route to our desired targets **3** and we commenced (Scheme 1) by transforming 6-methoxytetralone† **8** into the homologous aldehyde **9** by treatment with trimethylsulfoxonium iodide and sodium hydride in DMSO.[4] Oxidation of the aldehyde **9** to the corresponding acid[5] was readily effected with chromic acid in aqueous acetone, and the corresponding acid chloride **10** was prepared in standard fashion. This acid chloride was then reacted with phenylacetylene in the presence of aluminium chloride, and we were pleased to obtain the spirodienone **11a**, as the major product (53%); the cyclohexadienone and cyclopentenone units were characterised by ν_{max} 1703 (cyclopentenone C=O), 1661 and 1599 cm^{-1}, and δ_H 6.42 (m, 2-H, 4-H), 6.78 (s, 12-H) and 6.79 (d, 1-H). This sequence required acylation of the alkyne, intramolecular substitution by the

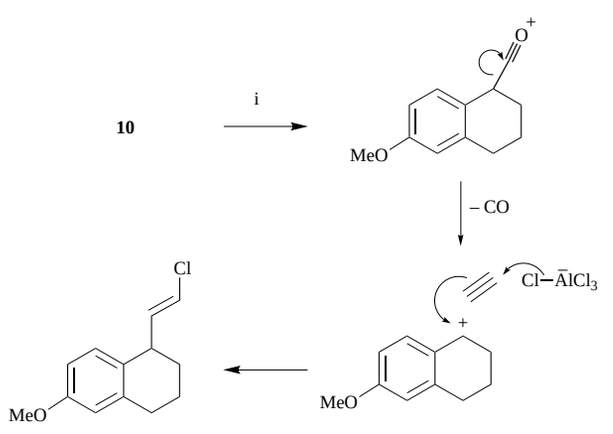


† IUPAC names for tetralin and tetralone are 1,2,3,4-tetrahydronaphthalene and 3,4-dihydronaphthalen-1(2*H*)-one, respectively. IUPAC names are given in the Experimental section for the compounds prepared in this paper.



Scheme 1 *Reagents:* i, $Me_3SO^+I^-$, NaH, DMSO; ii, CrO_3, H_2O, Me_2CO; iii, $(COCl)_2$, DCM, DMF; iv, phenylacetylene (*a*) or heptyne (*b*), $AlCl_3$, CH_2Cl_2

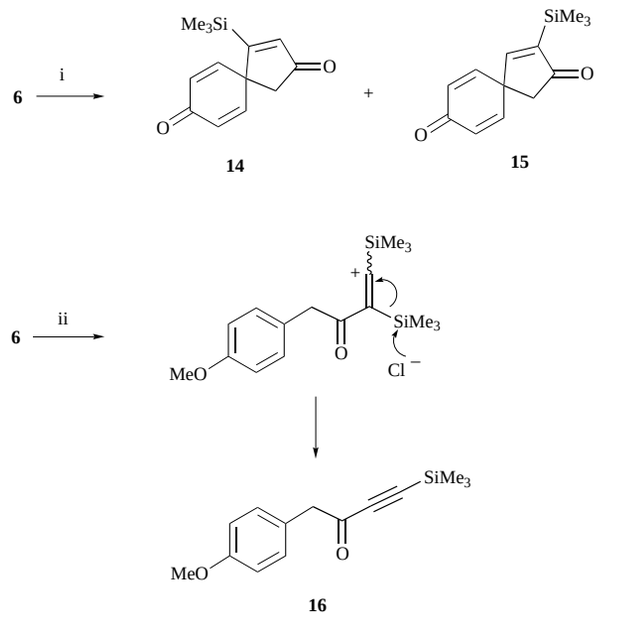
intermediate vinyl cation, and *O*-demethylation, as summarised in **12**. A parallel reaction with hept-1-yne provided the dienone **11b** (47%), but attempts to produce a similar tricyclospirodienone using ethyne were frustrated; instead the chief product was the tetrahydronaphthyl vinyl chloride **13**. Presumably, in this case the addition of the acyl cation to ethyne is relatively slow, and is superseded by decarbonylation to the more stable benzylic cation, which then proceeds to add to the alkyne, as illustrated in Scheme 2. In an attempt to circumvent this



Scheme 2 *Reagent:* i, $AlCl_3$, ethyne, CH_2Cl_2

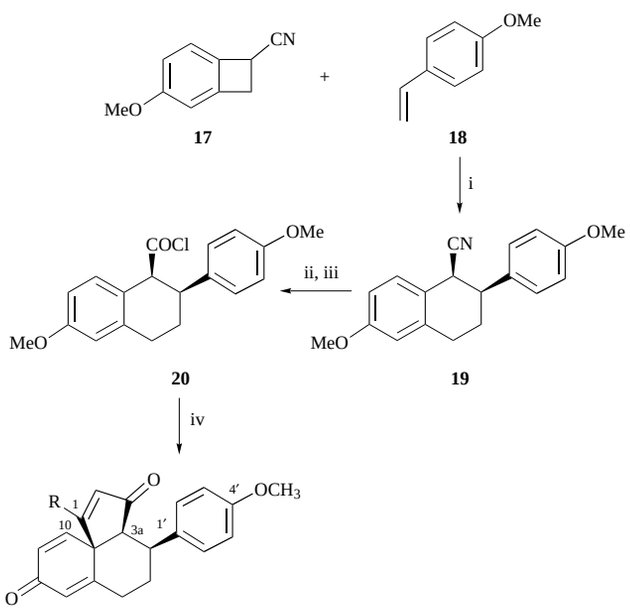
problem the reaction was repeated employing trimethylsilyl ethyne and bis(trimethylsilyl)ethyne, with 4-methoxyphenylacetyl chloride **6** as reacting partner (Scheme 3). In the first case both possible spirodiones **14** and **15** were isolated, in poor yields (11 and 19% respectively). The apparent lack of regiospecificity was surprising, but speculation about the reasons for this are premature, since the low yields and poor mass balance mask the complete product picture. With bis(trimethylsilyl)ethyne, no spirocyclisation was observed; the only product which could be isolated was the acylated alkyne **16**, 52%, formed as indicated.

We then turned our attention to applying this chemistry to



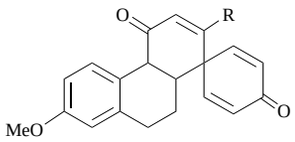
Scheme 3 *Reagents:* i, $AlCl_3$, $Me_3Si{-}C{\equiv}C{-}H$, CH_2Cl_2; ii, $AlCl_3$, $Me_3Si{-}C{\equiv}C{-}SiMe_3$, CH_2Cl_2

aryltetralin compounds, in the hope of forming aryltricyclospirodienones of the target type **3**. The chosen route is outlined in Scheme 4, and relied on the thermal electrocyclic opening of



Scheme 4 *Reagents:* i, 175 °C; ii, KOH, 180 °C; iii, $(COCl)_2$, DMF; iv, $AlCl_3$, $R{-}C{\equiv}CH$, CH_2Cl_2

the benzocyclobutene **17**[6] with trapping of the product by the styrene **18** in a Diels–Alder process.[7] This reaction gave the *cis*-nitrile **19** (55%) which was hydrolysed to the corresponding acid. The derived acid chloride **20** reacted smoothly with each of phenylacetylene, pent-1-yne and hept-1-yne to afford the aryltricyclospirodienones **21a–c**, respectively, in fair yield. The possible isomers of type **22** were excluded by spectroscopic evidence, *e.g.* compound **21a** displayed ν_{max} 1703, 1661 and 1606 cm^{-1}. The *cis* stereochemistry formed in the adduct **19** was preserved in the products **21**. This was shown by the ^1H NMR spectra. Thus in **21a**, $J_{3a,4}$ 6.3 Hz was measured; this is concordant with a H–C(3a)–C(4)–H dihedral angle of *ca.* 30° as



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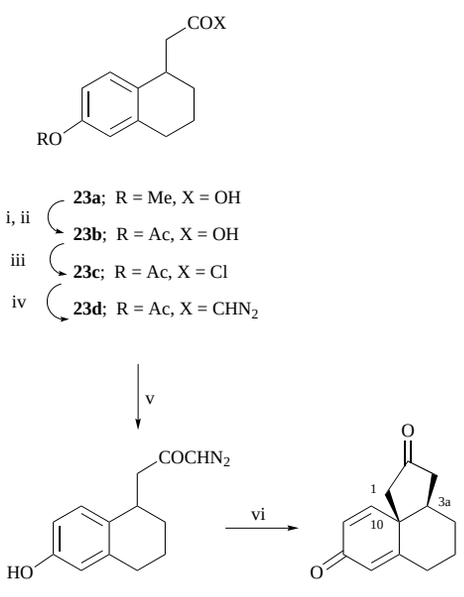
observed in the (energy minimised) preferred conformation (*cf.* **5**) where the C(8) substituent is equatorial in a quasi-boat ring. In contrast the H–C(3a)–C(4)–H dihedral in the *trans* isomer (*cf.* **4**) is close to 180°.

These products **21** are themselves not ideal as aromatase inhibitors, since they carry unsuitable phenyl or *n*-alkyl residues; however they did in fact show moderate activity in the micromolar range. The failure of the cationic spiroannulation to proceed with ethyne itself, or with mono- or bis-(trimethylsilyl)-ethyne prevented access to more desirable compounds unsubstituted at C-11, and further progress with this general strategy depends on alternative spirocyclisation tactics. To this end we investigated a longer and more conventional approach. Thus, 1-carboxymethyl-6-methoxytetralin **23a** was demethylated with trimethylsilyl iodide and the crude product was acetylated to provide the acetoxy acid **23b**; formation of the acid chloride **23c** and the diazo ketone **23d** proceeded uneventfully using standard methods, and the last was deacetylated to afford the phenolic diazo ketone **24**. Treatment of this product with boron



Scheme 5 *Reagents:* i, Me_3SiCl, NaI; ii, Ac_2O; iii, $(COCl)_2$, DCM, DMF; iv, CH_2N_2, Et_2O, PhMe; v, aq. Na_2CO_3, $NaHCO_3$; vi, BF_3, Et_2O

trifluoride–diethyl ether[8] then gave the required tricyclic diketone **25**, 62%, as a crystalline solid. It can be envisaged that this methodology could be applied to β-aryltetralin starting compounds, and if the cyclopentanone carbonyl in such products did prove to be amenable to preferential and regioselective manipulation, a valuable range of inhibitors might result. However this must remain for future investigations.

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 an internal TMS standard; multiplicities in ^{13}C NMR were obtained using a DEPT sequence. Observed splittings (*J*) are given in Hz. Mass spectra were obtained using electron impact or chemical ionisation methods. 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 40–60 °C. 'Evaporation' refers to evaporation under reduced pressure; 'washed' indicates the use of water and saturated aq. sodium hydrogen carbonate as appropriate; 'dried' implies the use of magnesium sulfate. 'Chromatography' means column chromatography using silica gel 60; eluting solvents are listed.

Reaction of 6-methoxy-1-chloroformyl-1,2,3,4-tetrahydronaphthalene with alkynes

(*a*) 6-Methoxy-1-carboxytetralin[5] was prepared through the corresponding aldehyde **9**.[4] The derived acid chloride (100 mg, 0.4 mmol) was dissolved in dichloromethane (5 ml) with phenylacetylene (0.09 ml, 0.8 mmol). The solution was cooled to 0 °C and aluminium chloride (0.16 g, 1.2 mmol) was added in portions over 5 min. The mixture was stirred at 0 °C for 1 h, when it was quenched with ice water and extracted with diethyl ether. The organic phases were combined, washed, dried and evaporated. The residual oil was chromatographed on Florisil (0–50% ethyl acetate in hexane) to afford (3aR*,10aR*)-1-*phenyl*-3,3a,4,5,6,8-*hexahydrocyclopenta*[d]*naphthalene*-3,8-*dione* **11a** (47 mg, 43%) (Found: *m/z* 276.115. $C_{19}H_{16}O_2$ requires *M*, 276.115); ν_{max}(film)/cm^{-1} 1703, 1661, 1599; δ_H 1.54–1.78 (3H, m, 5-CH_2, 4-CH_{ax}), 2.05 (1H, m, 4-CH_{eq}), 2.30 (1H, m, 6-CH_{eq}), 2.47 (1H, m, 6-CH_{ax}), 2.85 (1H, m, 3a-CH), 6.42 (2H, m, 9-CH, 7-CH), 6.78 (1H, s, 2-CH), 6.79 (1H, d, *J* 9.5, 10-CH), 7.33–7.49 (5H, m, PhH); δ_C 16.67, 24.23, 29.34 (4-CH_2, 5-CH_2, 6-CH_2), 55.11 (10a-C), 56.47 (3a-CH), 126.55 (2′-CH), 128.50 (3′-CH), 128.75, 129.08 (7-CH, 2-CH), 130.69, 131.03 (9-CH, 4′-CH), 132.76 (1′-C), 151.42 (10-CH), 161.24, 174.38 (6a-C, 1-C), 185.36, 207.34 (8-C, 3-C).

(*b*) The above acid chloride (100 mg, 0.4 mmol) was reacted with hept-1-yne (0.11 ml, 0.8 mmol) and aluminium chloride (0.16 g, 1.2 mmol) in dichloromethane (5 ml) as described above, and the product was isolated and purified in parallel fashion to afford (3aR*,10aR*)-1-*pentyl*-3,3a,4,5,6,8-*hexahydrocyclopenta*[d]*naphthalene*-3,8-*dione* **11b** (51 mg, 47%) (Found: *m/z* 270.163. $C_{18}H_{22}O_2$ requires *M*, 270.162); ν_{max}(film)/cm^{-1} 1710, 1664, 1616; δ_H 0.89 (3H, m, Me), 1.62 (12H, br, linear-CH_2, 5-CH_2, 4-CH_2), 2.35 (2H, m, 6-CH_2), 2.72 (1H, m, 3a-CH), 6.37 (4H, br m, 2-CH, 7-CH, 9-CH, 10-CH); δ_C 13.67 (18-Me), 19.07, 22.14, 23.18, 26.64, 28.66, 29.08, 31.12 (7 × CH_2), 54.07 (3a-CH), 56.79 (10a-C), 129.38, 129.69 (7-CH, 2-CH), 131.09 (9-CH), 150.61 (10-CH), 160.24, 181.88 (6a-C, 1-C), 185.91, 208.53 (8-C, 3-C).

(*c*) The above acid chloride (0.5 g, 2.23 mmol) was dissolved in dichloromethane (5 ml). Ethyne was bubbled through the solution for 1 min which then was stirred under ethyne for 15 min before cooling to 0 °C, when aluminium chloride (0.9 g, 6.68 mmol) was added in portions during 5 min. The mixture was stirred at 0 °C for 1 h, when it was quenched with ice–water and extracted with diethyl ether. The product was isolated and purified as above to yield 1-(2-*chlorovinyl*)-6-*methoxy*-1,2,3,4-*tetrahydronaphthalene* **13** (285 mg, 58%) as a yellowish oil (Found: *m/z* 222.083. $C_{13}H_{15}ClO$ requires *M*, 222.081); ν_{max}(film)/cm^{-1} 3060, 1608, 1577; δ_H 1.69 (2H, m, 3-CH_2), 1.90 (2H, m, 2-CH_2), 2.73 (2H, m, 4-CH_2), 3.4 (1H, ddd, each *J ca.* 6.2, 1-CH), 3.77 (3H, s, CH_3O), 5.94 (2H, m, CH=CH), 6.62 (1H, d, *J* 2.6, 5-CH), 7.70 (1H, dd, *J* 2.6, 8.4), 7.02 (1H, d, *J* 8.4); δ_C 20.48, 29.76, 29.99 (2-CH_2, 3-CH_2, 4-CH_2), 40.43 (1-CH), 55.20 (CH_3O), 112.07 (5-CH), 113.74 (7-CH), 117.84 (*C*H=CHCl), 129.03, 138.19 (4a-C, 8a-C), 130.33 (8-CH), 138.42 (CH=*C*HCl), 158.00 (6-C).

Reaction of 4-methoxyphenylacetyl chloride with alkynes

(*a*) Anhydrous aluminium chloride (2.2 g, 16.4 mmol) was added in portions to a stirred solution of 4-methoxyphenylacetyl chloride (2.0 g, 10.9 mmol) and hex-1-yne (0.9 g, 10.9

mmol) in dichloromethane (40 ml) at 0 °C. The mixture was stirred for 1 h under nitrogen and then quenched with ice (40 g). The mixture was poured into water and extracted with dichloromethane. The organic extracts were combined, washed, dried and evaporated. The residual brown solid was purified by chromatography (80% diethyl ether–20% light petroleum) to afford 4-*butylspiro*[4.5]*deca*-3,6,9-*triene*-2,8-*dione* **7**; R = Bu (1.08 g, 46%) as a crystalline solid, mp 119–120 °C (Found: C, 77.55; H, 7.57; *m/z* 216.144. $C_{14}H_{16}O_2$ requires C, 77.75; H, 7.46%; *M*, 216.115); ν_{max}/cm^{-1} 1721, 1698, 1659, 1622; δ_H 0.90 (3H, t, *J* 7.3, Me), 1.32 (2H, m, CH_2), 1.52 (2H, m, CH_2), 2.10 (2H, t, *J* 6.9, CH_2), 2.65 (2H, s, CH_2), 6.22 (1H, s, CH), 6.44 (2H, d, 10.1, 2 × CH), 6.66 (2H, d, *J* 10.1, 2 × CH); δ_C 13.59 (Me), 22.09, 28.65, 29.42, 44.89 (4 × CH_2), 52.45 (C), 130.44 (3 × CH), 149.83 (2 × CH), 181.42 (C), 184.69, 204.38 (2 × C=O).

(*b*) Aluminium chloride (0.65 g), 4-methoxyphenylacetyl chloride (0.6 g) and trimethylsilylacetylene (0.32 g) were reacted together in dichloromethane (15 ml) as in the preceding experiment. The products were isolated in parallel fashion and separated by column chromatography (50% diethyl ether–50% light petroleum) to yield (*i*) 4-*trimethylsilylspiro*[4.5]*deca*-3,6,9-*triene*-2,8-*dione* **14** (83 mg, 11%) as a yellow amorphous solid (Found: *m/z* 232.094. $C_{13}H_{16}O_2Si$ requires *M*, 232.092); ν_{max}(film)/cm^{-1} 1754, 1721, 1662, 1610; δ_H 0.14 (9H, s, $SiMe_3$), 2.56 (2H, s, CH_2), 6.39 (2H, d, *J* 10, 2 × CH), 6.56 (1H, s, CH), 6.69 (2H, d, *J* 10, 2 × CH), and (*ii*) 3-*trimethylsilylspiro*[4.5]-*deca*-3,6,9-*triene*-2,8-*dione* **15** (145 mg, 19%) also as a yellow amorphous solid (Found: *m/z* 232.093. $C_{13}H_{16}O_2Si$ requires *M*, 232.092); ν_{max}(KBr)/cm^{-1} 1697, 1660, 1622; δ_H 0.22 (9H, s, $SiMe_3$), 2.62 (2H, s, CH_2), 6.37 (2H, d, *J* 10, 2 × CH), 6.66 (2H, d, *J* 10, 2 × CH), 7.10 (1H, s, CH); δ_C −1.91 ($SiMe_3$), 45.22 (CH_2), 51.47 (C), 129.85 (2 × CH), 149.44 (C), 149.91 (2 × CH), 169.88 (CH), 184.80, 209.53 (2 × C=O).

(*c*) A parallel experiment using bis(trimethylsilyl)acetylene afforded a crude orange oil which was chromatographed (0–50% diethyl ether–light petroleum) to provide 4-*trimethylsilyl*-1-(4-*methoxyphenyl*)*but*-3-*yn*-2-*one* **16** (0.39 g, 52%) as an oil (Found: *m/z* 246.104. $C_{14}H_{18}O_2Si$ requires *M*, 246.107); ν_{max}/cm^{-1} 2150, 1675, 1612; δ_H 0.2 (9H, s, $SiMe_3$), 3.77 (2H, s, CH_2), 3.79 (3H, s, OMe), 6.87 (2H, d, *J* 8.8, 2 × CH), 7.15 (2H, d, *J* 8.8, 2 × CH); δ_C −1.19 ($SiMe_3$), 50.75 (CH_2), 54.76 (OMe), 99.17, 101.59 (2 × C), 113.76 (2 × CH), 124.57 (C), 130.56 (2 × CH), 158.68 (C), 184.58 (C=O).

cis-1-Cyano-2-(4-methoxyphenyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene 19

1-Cyano-3-methoxy-1,2-dihydrobenzocyclobutene[6] (10 g, 63 mmol) and 4-vinylanisole (14.8 ml, 110 mmol) were heated together at 175 °C for 45 min under nitrogen. The cooled mixture was taken up in a minimum volume of dichloromethane and chromatographed on silica using 10% ethyl acetate–hexane. The major product was a yellow solid, recrystallised from ethanol to yield the *title compound* **19** as white crystals (10.2 g, 55%), mp 119–120 °C (Found: *m/z* 293.142. $C_{19}H_{19}O_2N$ requires M, 293.142); ν_{max}/cm^{-1} 2239, 1613; δ_H 2.15 (2H, m, 3-CH_2), 2.97 (2H, m, 4-CH_2), 3.75 (1H, m, 2-CH), 3.80 (6H, s, 2 × MeO), 4.07 (1H, m, 1-CH), 6.80 (3H, m, 5-CH, 7-CH, 8-CH), 7.20 (4H, br s, 4 × ArH).

Reaction of *cis*-1-chloroformyl-2-(4-methoxyphenyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene 20 with alkynes

The above nitrile (4 g, 13.7 mmol) was heated in ethylene glycol (100 ml) at 180 °C for 12 h with potassium hydroxide (20 g). The cooled solution was acidified, and the precipitated acid was collected, dried and recrystallised from ethyl acetate–light petroleum to afford cis-1-*carboxy*-2-(4-*methoxyphenyl*)-6-*methoxy*-1,2,3,4-*tetrahydronaphthalene* as white crystals (1.23 g, 29%), mp 203–205 °C (Found: *m/z* 312.136. $C_{19}H_{20}O_4$ requires *M*, 312.136). The acid was converted into the corresponding *acid chloride* **20** in standard manner using oxalyl chloride and dimethylformamide.

(*a*) The acid chloride **20** (200 mg, 0.6 mmol) and phenylacetylene (0.13 ml, 1.2 mmol) were dissolved in dichloromethane (5 ml) under nitrogen, and the solution was cooled to 0 °C. Aluminium chloride (0.24 g, 1.8 mmol) was added over 5 min with stirring, and the mixture was stirred for 1 h at 0 °C, when it was quenched with ice–water and extracted with diethyl ether. The organic phases were combined, washed, dried and evaporated. The residual oil was chromatographed on Florisil (0–100% ethyl acetate in hexane). The most polar fractions yielded (3aR*,4R*,10aR*)-4-(4′-*methoxyphenyl*)-1-*phenyl*-3,3a,4,5,6,8-*hexahydrocyclopenta*[d]*naphthalene*-3,8-*dione* **21a** as a yellowish oil (100 mg, 44%) (Found: *m/z* 382.157. $C_{26}H_{22}O_3$ requires *M*, 382.157); ν_{max}(film)/cm^{-1} 1703, 1661, 1606, 1571; δ_H 1.98 (1H, m, 5-CH), 2.10 (1H, m, 5-CH), 2.26 (1H, dt, *J* 6, 14.4, 6-CHa), 2.49 (1H, dt, *J* 6, 14.4, 6-CHb), 3.07 (1H, d, *J* 6.3, 3a-CH), 3.24 (1H, m, 4-CH), 3.77 (3H, s, MeO), 6.30 (1H, s, 7-CH), 6.43 (1H, dd, *J* 1.6, 9.8, 9-CH), 6.64 (1H, s, 2-CH), 6.72 (1H, d, *J* 9.7, 10-CH), 6.81 (2H, d, *J* 8.7, Ar-H_2), 7.04 (2H, d, *J* 8.7, Ar-H_2), 7.36 (5H, br m, Ph-H_5); δ_C 30.35 (5-CH_2), 31.44 (6-CH_2), 42.11 (4-CH), 54.88 (MeO), 55.00 (10a-C), 61.94 (3a-CH), 113.54 (2′-CH), 126.68 (2″-CH), 128.15 (3′-CH), 128.62 (3″-CH), 128.85, 129.31 (7-CH, 2-CH), 129.80, 130.98 (9-CH, 4″-CH), 132.79, 132.92 (1″-C, 1′-C), 152.41 (10-CH), 158.14 (4′-C), 160.54, 173.66 (6a-C, 1-C), 185.61, 205.81 (8-C, 3-C).

(*b*) The above acid chloride (211 mg, 0.64 mmol) was reacted with pent-1-yne (0.13 ml, 1.28 mmol) and aluminium chloride (0.26 g, 1.92 mmol) in dichloromethane (5 ml) as described above, and the product was isolated and purified in parallel fashion to afford (3aR*,4R*,10aR*)-4-(4′-*methoxyphenyl*)-1-*propyl*-3,3a,4,5,6,8-*hexahydrocyclopenta*[d]*naphthalene*-3,8-*dione* **21b** as a yellowish oil (70 mg, 31%) (Found: *m/z* 348.173. $C_{23}H_{24}O_3$ requires *M*, 348.173); ν_{max}(film)/cm^{-1} 1705, 1662, 1616; δ_H 0.93 (3H, t, *J* 7.3, *Me*CH_2), 1.57 (2H, m, 5-CH_2), 1.95 (4H, br m, 2 × CH_2), 2.32 (1H, m, 6-CHa), 2.51 (1H, *J* 6.4, 15.5, 6-CHb), 2.99 (1H, d, *J* 5.6, 3a-CH), 3.22 (1H, br dd, *J* 5.5, 12.1, 4-CH), 3.75 (3H, s, OMe), 6.28 (2H, s, 7-CH, 2-CH), 6.36 (1H, dd, *J* 1.6, 9.6, 9-CH), 6.43 (1H, d, *J* 9.6, 10-CH), 6.78 (2H, d, *J* 8.7, Ar-H), 7.00 (2H, d, *J* 8.7, Ar-H); δ_C 13.68 (CH_2CH_3), 20.34, 28.66 ($CH_2CH_2CH_3$), 30.43 (6-CH_2, 5-CH_2), 41.46 (4-CH), 55.15 (OMe), 56.03 (10a-C), 59.23 (3a-CH), 113.76 (2′-CH), 128.30 (3′-CH), 128.73, 129.68 (7-CH, 2-CH), 129.98 (9-CH), 133.62 (1′-C), 151.35 (10-CH), 158.33 (4′-C), 159.98, 180.40 (6a-C, 1-C), 207.25 (8-C, 3-C).

(*c*) The above acid chloride (200 mg, 0.6 mmol) was reacted with hept-1-yne (0.16 ml, 1.2 mmol) and aluminium chloride (0.24 g, 1.8 mmol) in dichloromethane (5 ml) as described above, and the product was isolated and purified in parallel fashion to afford (3aR*,4R*,10aR*)-4-(4-*methoxyphenyl*)-1-*pentyl*-3,3a,4,5,6,8-*hexahydrocyclopenta*[d]*naphthalene*-3,8-*dione* **21c** as a colourless oil (73 mg, 32%) (Found: *m/z* 376.204. $C_{25}H_{28}O_3$ requires *M*, 376.204); ν_{max}(film)/cm^{-1} 1705, 1662, 1616; δ_H 0.88 (3H, t, *J* 6.8, *Me*CH_2), 1.28 (4H, br m, 2 × CH_2), 1.54 (2H, m, 5-CH_2), 1.96 (4H, br m, 2 × CH_2), 2.31 (1H, m, 6-CHa), 2.51 (1H, dt, *J* 6.4, 15.4, 6-CHb), 2.99 (1H, d, *J* 5.6, 3a-CH), 3.22 (1H, br dd, $J_{3a,4}$ 5.6, $J_{4,5ax}$ 12.1, 4-CH), 3.75 (3H, s, OMe), 6.28 (2H, br s, 7-H, 2-H), 6.35 (1H, dd, *J* 1.5, 9.7, 9-CH), 6.77 (2H, d, *J* 8.7, Ar-H), 7.00 (2H, d, *J* 8.7, Ar-H); δ_C 13.62 (CH_2CH_3), 22.08, 26.45, 27.94, 28.51 (4 × CH_2), 30.20, 31.00 (6-CH_2, 5-CH_2), 41.21 (4-CH), 54.90 (OMe), 55.82 (10a-C), 59.00 (3a-CH), 113.52 (2′-CH), 128.05 (3′-CH), 128.49, 128.86 (7-CH, 2-CH), 129.73 (9-CH), 133.38 (1′-C), 151.12 (10-CH), 158.08 (4′-C), 159.73, 180.43 (6a-C, 1-C), 185.82, 207.00 (8-C, 3-C).

6-Acetoxy-1-carboxymethyl-1,2,3,4-tetrahydronaphthalene 23b

1-Carboxymethyl-6-methoxy-1,2,3,4-tetrahydronaphthalene **23a** (prepared by the method of Haberland[9]) (8.98 g, 40.8

mmol) in acetonitrile (80 ml) was treated with trimethylchlorosilane (25.9 ml, 200 mmol) and sodium iodide (12.23 g, 80 mmol). The mixture was refluxed for 2 h, cooled and poured into water. The organic products were extracted into diethyl ether, and the diethyl ether phase was extracted with saturated aq. sodium carbonate. The aq. alkaline extracts were acidified and in turn extracted with diethyl ether. The ethereal layers were washed, dried and evaporated to give the crude phenolic acid as a pale brown oil. This product was dissolved in pyridine (20 ml) and acetic anhydride (20 ml, 0.21 mol), and the solution was set aside overnight when it was evaporated. The residue was stirred in methanol (50 ml) and water (50 ml) for 1 h, when the bulk of the methanol was removed under reduced pressure. The remaining aqueous material was extracted into diethyl ether, and the extracts were washed with saturated aq. sodium carbonate. The aq. alkaline extracts were acidified and extracted with diethyl ether. The diethyl ether phase was treated with decolourising charcoal, washed, dried and evaporated to provide after chromatography (40% ethyl acetate in hexane) the *title acid* **23b** as a pale yellow oil (2.64 g, 26%) (Found: *m/z* 253.992. $C_{14}H_{16}O_4$ requires *M*, 253.994); ν_{max}/cm^{-1} 3500–2700 (broad), 1760, 1715; δ_H 1.82 (4H, br m, 2-CH_2, 3-CH_2), 2.34 (3H, s, CH_3CO_2), 2.86 (4H, br m, 4-CH_2, CH_2CO_2), 2.94 (1-H, m, 1-CH), 6.76 (1H, br s, 5-CH), 6.81 (1H, dd, *J* 3, 9, 7-H), 7.15 (1H, d, *J* 9, 8-H).

6-Acetoxy-1-(3-diazo-2-oxopropyl)-1,2,3,4-tetrahydronaphthalene 23d

6-Acetoxy-1-carboxymethyl-1,2,3,4-tetrahydronaphthalene **23b** (2.64 g, 10 mmol) in dichloromethane (30 ml) containing dimethylformamide (0.15 ml) at −20 °C was treated with oxalyl chloride (1.86 ml, 20 mmol) and the mixture was stirred for 2 h at −20 °C. The product was then evaporated to dryness to yield the crude acid chloride which was dissolved in toluene (10 ml). This solution was added dropwise to ethereal diazomethane (1.05 g, 25 mmol) at 0 °C, and the mixture was then set aside overnight at room temperature. The excess diazomethane and the diethyl ether solvent were then removed in a stream of argon. The residue was chromatographed on Florisil (20% ethyl acetate in hexane) to afford the *title diazo ketone* as a yellow waxy solid (383 mg, 15%), ν_{max}/cm^{-1} 2100, 1743, 1645; δ_H 1.80 (4H, br m, 2-CH_2, 3-CH_2), 2.27 (3H, s, CH_3CO_2), 2.66 (4H, br m, 4-CH_2, CH_2CO), 3.41 (1H, m, 1-CH), 5.20 (1H, s, $COCHN_2$), 6.81 (2H, m, 5-CH, 7-H), 7.16 (1H, d, *J* 8.4, 8-H); δ_C 19.29, 28.05, 29.56 (C-2, C-3, C-4), 21.12 (Me), 34.04 (C-1), 48.31 (*C*-CO), 55.21 (CHN_2), 119.05, 121.79 (C-5, C-7), 129.36 (C-8), 137.05, 138.58 (C-4a, C-8a), 148.61 (*C*$OCHN_2$), 169.77 (C-6), 193.91 (Me*C*O_2).

1-(3-Diazo-2-oxopropyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalene 24

6-Acetoxy-1-(3-diazo-2-oxopropyl)-1,2,3,4-tetrahydronaphthalene **23d** (380 mg, 1.48 mmol) was dissolved in methanol (5 ml) and mixed with a solution of sodium carbonate (0.31 g, 2.97 mmol) and sodium hydrogen carbonate (0.37 g, 4.45 mmol) in water (4 ml). The mixture was stirred at ambient temperature for 2 h, when it was diluted with water (50 ml) and the pH was adjusted to 7.5 by addition of dilute aq. oxalic acid. The final mixture was extracted with diethyl ether. The combined diethyl ether layers were dried and evaporated to afford the *title diazo ketone* (293 mg, 86%) as a yellow amorphous solid (Found: *m/z* 202.0996. $C_{13}H_{14}O_2N_2$ requires $M - N_2$, 202.0994); ν_{max}/cm^{-1} 3400–3300, 2100, 1620; δ_H 1.80 (4H, br m, 2-CH_2, 3-CH_2), 2.70 (4H, br m, 4-CH_2, CH_2CO), 3.35 (1-H, m, 1-CH), 4.87 (1H, s, OH), 5.25 (1H, s, $COCHN_2$), 6.58 (1H, br s, 5-CH), 6.65 (1H, dd, *J* 3.9, 7-H), 7.08 (1H, d, *J* 9, 8-H).

(3a*R**,10a*S**)-1,2,3,3a,4,5,6,8-Octahydrocyclopenta[*d*]naphthalene-2,8-dione 25

Boron trifluoride–diethyl ether (0.25 ml) was added to a vigorously stirred solution of the above diazo ketone (100 mg, 0.4 mmol) in dry dichloromethane (5 ml) at ambient temperature under nitrogen, and stirring was maintained for 15 min. Water (1 ml) was then added to the reaction mixture, with stirring, followed after 5 min by brine (10 ml). The mixture was extracted with ethyl acetate, and the organic phases were combined, washed, dried and evaporated. The residual oil was chromatographed on Florisil (gradient elution with 10–100% ethyl acetate–hexane). The fractions containing the most polar product were evaporated to afford the *title spirodienone* as a yellow crystalline solid (50 mg, 62%), mp 118–120 °C (Found: *m/z* 202.0997. $C_{13}H_{14}O_2$ requires *M*, 202.0994); ν_{max}(film)/cm^{-1} 1745, 1661, 1620; δ_H 1.45 (2H, m, 5-CH_2), 1.94 (1H, m, 4-CHa), 2.06 (1H, m, 4-CHb), 2.10 (1H, d, *J* 19, 1-CHa), 2.21 (1H, d, *J* 19, 1-CHb), 2.36 (1H, m, 3a-CH), 2.44 (1H, dd, *J* 4, 12, 6-CHa), 2.52 (1H, d, *J* 12, 6-CHb), 2.81 (2H, m, 3-CH_2), 6.26 (1H, d, *J* 1.8, 7-CH), 6.28 (1H, dd, *J* 1.8, 10.1, 9-CH), 6.94 (1H, d, *J* 10.1, 10-CH); δ_C 26.64, 29.72, 32.10 (4-CH_2, 5-CH_2, 6-CH_2), 42.81 (3a-CH), 43.69, 44.77 (1-CH_2, 3-CH_2), 46.92 (10a-C), 126.65 (7-CH), 127.57 (9-CH), 150.31 (10-CH), 161.69 (6a-C), 185.46 (8-C), 214.32 (2-C).

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