Control of stereochemistry in an intramolecular Diels–Alder reaction by the phenylsulfonyl group; an improved synthesis of pisiferol

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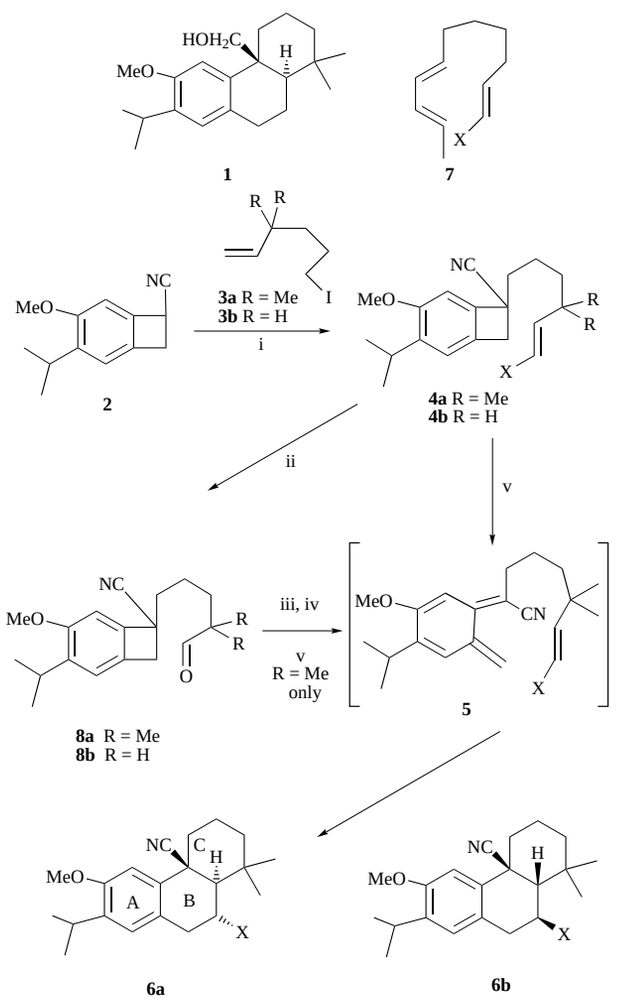
Thermolysis of 4a (X = H) gives 6a and 6b (X = H) in a ratio of 1:4 whereas 4b (X = SO_2Ph) gives more of the *trans*-ring junction product 6a (X = SO_2Ph) suitable for the synthesis of pisiferol [ratio 6a:6b (X = SO_2Ph) = 1.5:1]. Base catalysed elimination of the phenylsulfonyl group from 6a (X = SO_2Ph) gives 18 which is hydrogenated to 6a (X = H), an intermediate in the synthesis of pisiferol. Both 6a and 6b (X = SO_2Ph) have ring B in a half-boat conformation.

Kametani *et al.*[1] have described the synthesis of pisiferol methyl ether **1** starting with alkylation of the benzocyclobutene **2** with the iodide **3a**. Thermolysis of the product **4a** (X = H) is believed to proceed *via* the (*Z*)-*o*-quinodimethane **5** (X = H) which undergoes intramolecular Diels–Alder addition (IMDA) to give the products **6a** and **6b** (X = H) with the pisiferic acid skeleton, in 80% yield. Unfortunately **6a** (X = H) with the required *trans*-BC ring junction is the minor product and **6b** (X = H) the major product (1:4 ratio). The stereochemical problem was corrected but at the expense of an additional sequence of seven reactions proceeding in 21% overall yield. The IMDA reactions of most *o*-quinodimethanes with a four carbon chain linking diene and alkene give *trans*-adducts *via exo*-addition of the connecting chain. Since these *o*-quinodimethanes lack a (*Z*)-cyano group, the observed *endo*-chain preference for **5** (X = H) can tentatively be ascribed to repulsion between an *exo*-orientated chain and the (*Z*)-cyano group.

Craig *et al.*[2] have used the bulky phenylsulfonyl group placed *trans* to the connecting chain as in **7** (X = SO_2Ph) to obtain mostly the product of *endo*-chain (*exo*-SO_2Ph) addition. In contrast, related systems with X = H give comparable quantities of *cis*- and *trans*-products. Craig suggests the SO_2Ph group prefers the less sterically demanding *exo*-position. With this background we argued that in **5** (X = SO_2Ph) steric repulsion between the (*Z*)-cyano group and an *exo*-directed SO_2Ph group might force the SO_2Ph *endo* and the connecting chain *exo* so that the desired *trans*-BC product **6a** (X = SO_2Ph) would be favoured. To test this notion **4a** (X = H) was cleaved to the aldehyde **8a** which gave **4a** (X = SO_2Ph) by reaction with $PhSO_2CH_2Li$ and elimination of the resulting alcohol (Scheme 1).

Thermolysis of **4a** (X = SO_2Ph) at 180 °C (3 h) gave **6a** (X = SO_2Ph) and **6b** (X = SO_2Ph) in a much improved *trans*:*cis* ratio of 1.5:1 and 67% yield. In addition to the desired adducts the thermolysis also provided the (*E*,*E*)-diene **9** (Y = CN, X = SO_2Ph) (*ca.* 23%). Although not reported by the earlier workers,[1] a similar quantity of **9** [Y = (*E*)-CN, X = H] is formed in the thermolysis of **4a** (X = H). These products arise *via* a 1,5-sigmatropic hydrogen shift in an (*E*)-*o*-quinodimethane intermediate as shown by the arrows in **10**. The size and π-electron accepting ability of the cyano group favour its inward conrotation[3] in competition with an alkyl chain. However the benzocyclobutene ring-opening will be reversible unless the 1,5-shift and IMDA reaction are fast. In the event of such reversibility the ratio of products will depend less on the torquoselectivity of ring-opening[4] as on the relative rates of the 1,5-shift and



Scheme 1 *Reagents and conditions*: i, NaH–DMF, 65 °C, 0.5 h; ii, OsO_4–THF–H_2O–$NaIO_4$, 20 °C, 7 h; iii, $PhSO_2Me$–BuLi–THF, −78 °C, 1 h; iv, $MeSO_2Cl$–Et_3N–THF, −5 °C, 14 h; v, *o*-dichlorobenzene, 180 °C, 3 h

IMDA reaction. The situation is therefore finely balanced and represents a potentially serious flaw in the use of benzocyclobutenes as sources of *o*-quinodimethanes for IMDA reactions.[5] For example we attempted to increase the *trans*:*cis* adduct ratio by using the larger CO_2Me group in place of CN in **4a** (X = SO_2Ph). The ester **11** was readily obtained by treating **4a** (X = SO_2Ph) with methanol saturated with hydrogen chloride. However thermolysis of **11** at 160 °C (48 h) gave only products **12** and **13** derived *via* 1,5-sigmatropic hydrogen shifts in the

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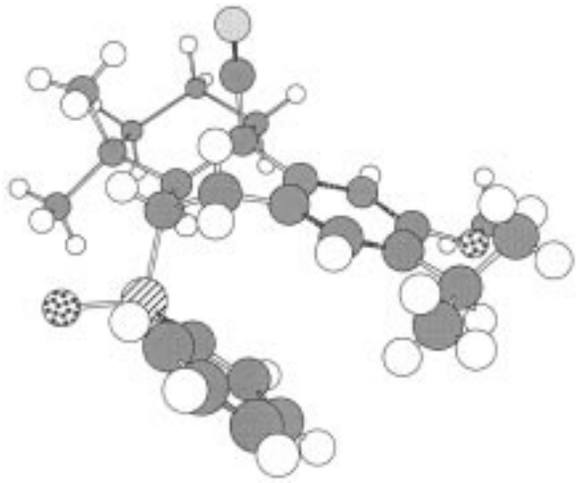
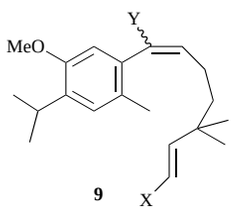


Fig. 1



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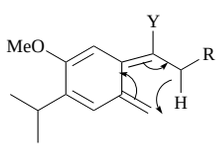

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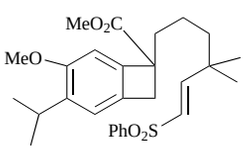

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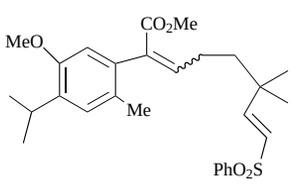
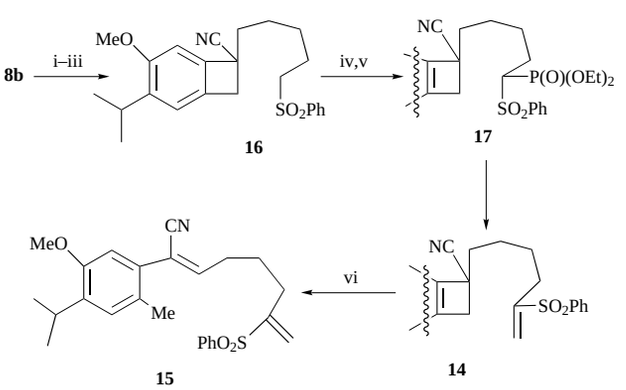


12 (*E*)-isomer
13 (*Z*)-isomer

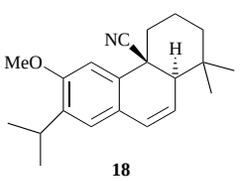
o-quinodimethane intermediate. A similar result attended our efforts to test the effect of an internal SO_2Ph group rather than a terminal one upon the *trans*:*cis* product ratio. For an internal SO_2Ph group the greater proximity of CN and SO_2Ph in the *exo*-SO_2Ph transition state was expected to favour *exo* disposition of the connecting chain. However thermolysis of **14** at 160 °C gave only the 1,5-shift product **15** and a dimeric product of unknown structure. The benzocyclobutene **14** was prepared as outlined in Scheme 2 starting with the aldehyde **8b** prepared as outlined in Scheme 1.



Scheme 2 *Reagents and conditions*: i, $NaBH_4$; ii, Ph_3P–CBr_4; iii, $PhSO_2Na$, HMPA, 20 °C; iv, LDA then $ClP(O)(OEt)_2$, −78 °C then HOAc; v, BuLi then $(HCHO)_n$; vi, 160 °C

The allocation of stereochemistry to **6a** and **6b** (X = SO_2Ph) was initially made on the basis of a very shielded methyl resonance (δ_H −0.26) in the NMR spectrum of **6b** (X = SO_2Ph) which was absent for **6a** (X = SO_2Ph). The spectra of both isomers show vicinal couplings for the ring-B protons suggesting both compounds prefer to exist with ring B in a half-boat conformation (Experimental section). The boat structure for **6a** (X = SO_2Ph) was confirmed by an X-ray structure determination (Fig. 1).[6] Existence of **6a** (X = SO_2Ph) in the boat-like conformation shown above is understandable as in the alternative half-chair conformation the SO_2Ph and nearby α-Me are much closer. For the half-chair conformation corresponding to **6b** (X = SO_2Ph) the SO_2Ph and CN groups would be 1,3-diaxial.

To complete the synthesis of pisiferol the sulfone **6a** (X = SO_2Ph) was heated in 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 130 °C (3 h) to give the alkene **18** (92% yield). Hydro-



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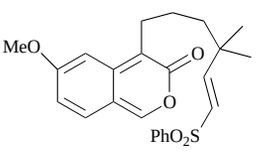

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genation of **18** over Pd–C gave **6a** (X = H) (*ca.* 98% yield) convertible into pisiferol by reduction, first by diisobutylaluminium hydride and then with sodium borohydride followed by sodium ethanethiolate mediated demethylation of the aryl ether.[1]

The improvement in the *trans*:*cis* adduct ratio and the pisiferol synthesis observed here raise interesting possibilities of similar control of the Diels–Alder reactions of other dienes with (*Z*)-substituents, including 1,4-bridged dienes, *e.g.* cyclopentadiene, cyclohexadiene, α-pyrone and furan. We have already shown the effect is important for the 2-benzopyran-3-one **19**.[7] The use of more bulky arylsulfonyl groups may be of value in extending these studies.

Experimental

Mps were determined with a Kofler hot-stage apparatus and are uncorrected. Infrared spectra were recorded on a Philips PU 8706 infrared spectrophotometer, and referenced to the peak at 1601 cm^{-1} of polystyrene. Ultraviolet and visible spectra were recorded on a Pye-Unicam PU 8800 UV–VIS spectrophotometer; log ε values are in parentheses. Unless otherwise stated ^1H NMR spectra were measured in $CDCl_3$ with tetramethylsilane as internal standard; 400 MHz NMR spectra were measured on a Bruker WH-400 instrument, and 300 MHz spectra on a General Electric Nicolet QE 300 spectrometer. All NMR absorbances are expressed in parts per million; coupling constants *J* are in Hz. Mass spectra were obtained on an Autospec mass spectrometer. Chromatography on silica refers to short-column chromatography over Kieselgel G60 (Merck).[8] Thin layer chromatography was carried out on glass plates (15 × 5 cm), dipped in an ethyl acetate suspension of Kieselgel G60 and dried in an air oven at 120 °C for at least one hour. Ether refers to diethyl ether and petroleum to the fraction bp 60–80 °C. 'Base-washed glassware' was soaked in 2 M aqueous potassium hydroxide (18 h), washed with water and acetone, and oven dried (120 °C, 16 h). All solvents were distilled and dried before use by standard procedures.[9] Unless otherwise stated, all reactions were conducted under an atmosphere of dry, oxygen-free argon. For procedures requiring anhydrous conditions all glassware was oven dried prior to use. Solvents were evaporated under reduced pressure using a Buchi rotary evaporator at water aspirator pressure followed by heating on a steam bath at water aspirator pressure.

Oxidative cleavage of 4a (X = H)

To a solution of the alkene[1] (2.19 g, 7.04 mmol) and OsO_4 (50 mg) in THF (20 ml) and water (7 ml) was added at room temp.

sodium metaperiodate (3.21 g, 15.2 mmol) in portions over 8 h. The mixture was stirred at 20 °C (2.5 h), poured into water, extracted (Et_2O), dried ($MgSO_4$) and concentrated. Chromatography on silica (120 g) in benzene–ether (24:1) gave 1-(4,4-dimethyl-5-oxopentyl)-4-isopropyl-5-methoxy-1,2-dihydrobenzocyclobutene-1-carbonitrile **8a** (1.28 mg, 58%) mp 109.5–110.0 °C (from dichloromethane–ethanol) (Found: C, 76.6; H, 8.4; N, 4.7. $C_{20}H_{27}NO_2$ requires C, 76.7; H, 8.6; N, 4.5%); ν_{max}(Nujol)/cm^{-1} 2220 and 1725; δ_H(300 MHz) 1.11 (6H, s, 2 × Me), 1.19 (6H, d, *J* 7.0, CH*Me*$_2$), 1.57 (4H, m), 1.94 (2H, m), 3.18 (1H, d, *J* 13.5, benzylic-H), 3.35 (1H, septet, *J* 7.0, C*H*Me$_2$), 3.64 (1H, d, *J* 13.5, benzylic-H), 3.83 (3H, s, OMe), 6.71 (1H, s, Ar-H), 7.01 (1H, s, Ar-H), 9.48 (1H, s, CHO); *m*/*z* 313 (M$^+$), 298, 270, 242, 214, 200, 198, 161, 43 and 41 (64.4, 70.5, 88.8, 72.2, 73.2, 100.0, 51.7, 75.6, 66.2 and 56.3%).

Preparation of 1-(4,4-dimethyl-6-phenylsulfonylhex-5-enyl)-4-isopropyl-5-methoxy-1,2-dihydrobenzocyclobutene-1-carbonitrile 4a (X = SO_2Ph)

To a stirred solution of methyl phenyl sulfone (1.55 g, 9.9 mmol) in dry THF (26 ml) under argon at −78 °C was added dropwise by syringe *n*-butyllithium (4.0 ml of a 2.5 M solution in hexanes, 9.9 mmol) to give a colourless solution of the anion. After 10 min a solution of the aldehyde **8a** (1.24 g, 3.97 mmol) in dry THF (25 ml) was added, rinsing with further THF (10 ml) at −78 °C. After 1 h the reaction was quenched by the addition of a solution of acetic acid in THF (20 ml of a 1.0 M solution, 20 mmol), stirred (10 min) and allowed to warm to 20 °C (0.5 h). The solution was poured into saturated aqueous $NaHCO_3$, extracted (CH_2Cl_2), washed (3 × H_2O), dried ($MgSO_4$) and concentrated to give a solid. Chromatography on silica (80 g) eluting initially with dichloromethane then changing to benzene–ether (4:1) gave the diastereomeric β-*hydroxy sulfones* (1.51 g, 81%) (Found: C, 69.0; H, 7.4; N, 2.8; S, 6.8. $C_{27}H_{35}NO_4S$ requires C, 69.1; H, 7.5; N, 3.0; S, 6.8%); ν_{max}(film)/cm^{-1} 3520, 2960 and 2220; δ_H(300 MHz) 0.85 (6H, s, 2 × Me), 0.88 (3H, s, Me), 0.89 (3H, s, Me), 1.19 (12H, d, *J* 7.0, CH*Me*$_2$), 1.42–1.67 (8H, m), 1.87 (4H, m), 3.10–3.37 (10H, m), 3.63 (2H, dd, *J* 3.0 and 13.5), 3.82 (6H, s, OMe), 3.93 (2H, t, *J* 10.5), 6.72 (1H, s, Ar-H), 6.74 (1H, s, Ar-H), 7.01 (2H, s, Ar-H), 7.58–7.71 (6H, m, SO_2Ph), 7.94–7.96 (4H, m, SO_2-Ph); *m*/*z* 469 (M$^+$), 270, 242, 216, 200, 199, 198, 77, 69 and 43 (53.8, 37.7, 100.0, 41.3, 37.6, 31.4, 36.0, 46.3, 36.1 and 37.1%).

To a stirred solution of the foregoing β-hydroxy sulfones (1.46 g, 3.1 mmol) in dry CH_2Cl_2 (45 ml) under argon at −10 °C was added dropwise by pipette triethylamine (3.11 g, 30.6 mmol) in dichloromethane (4 ml) followed by methanesulfonyl chloride (7 equiv. 2.47 g) in dichloromethane (4 ml). The reaction was stirred at −10 °C (16 h), then allowed to warm to room temp. and stirred (24 h). The mixture was poured into saturated aqueous ammonium chloride, extracted (CH_2Cl_2), washed with water, dried ($MgSO_4$) and concentrated to give an oil. Chromatography on silica (16 g) eluting with benzene–ether (19:1) gave the *sulfone* **4a** (X = SO_2Ph) (714 mg, 51%), mp 139.5–140.5 °C (from ethanol) (Found: C, 71.8; H, 7.5; N, 3.1; S, 6.9. $C_{27}H_{33}NO_3S$ requires C, 71.8; H, 7.3; N, 3.1; S, 7.1%); ν_{max}(film)/cm^{-1} 2950, 2220 and 1600; δ_H(300 MHz) 1.09 (3H, s, Me), 1.10 (3H, s, Me), 1.18 (6H, d, *J* 6.9, CH*Me*$_2$), 1.50 (4H, m), 1.88 (2H, m), 3.13 (1H, d, *J* 13.5, benzylic-H), 3.38 (1H, septet, *J* 7.0, C*H*Me$_2$), 3.61 (1H, d, *J* 13.5, benzylic-H), 3.82 (3H, s, OMe), 6.23 (1H, d, *J* 15.5, olefinic-H), 6.69 (1H, s, Ar-H), 6.96 (1H, d, *J* 15.5, olefinic-H), 7.01 (1H, s, Ar-H), 7.58 (3H, m, SO_2Ph), 7.89 (2H, m, SO_2Ph); *m*/*z* 452, 451 (M$^+$), 436, 242, 215, 214, 200, 199, 125 and 41 (27.7, 74.0, 52.9, 100.0, 40.3, 43.8, 44.8, 28.1, 26.8 and 28.1%).

Further elution of the column gave unreacted starting material **8a** (380 mg, 26%).

IMDA Addition of 4a (X = SO_2Ph)

A solution of the benzocyclobutene **4a** (X = SO_2Ph) (620 mg, 1.37 mmol) in *o*-dichlorobenzene (190 ml) was heated at reflux (3 h). Chromatography of the concentrated product on neutral alumina (18 g) (Fluka type 507C), eluting with benzene–ether (24:1) gave the exo-*chain adduct* 7-isopropyl-6-methoxy-1,1-dimethyl-10-phenylsulfonyl-1,2,3,4,4a,9,10,10a-octahydrophenanthrene-4a-carbonitrile **6a** (X = SO_2Ph) (192 mg, 31%), mp 153–154 °C (ethanol) (Found: M$^+$, 451.2195. $C_{27}H_{33}NO_3S$ requires *M*, 451.2181); ν_{max}(film)/cm^{-1} 2970 and 2220; δ_H(300 MHz) 1.15 (3H, d, *J* 6.9, CH*Me*$_2$), 1.23 (3H, s, Me), 1.25 (3H, d, *J* 7.0, CH*Me*$_2$), 1.36 (3H, s, Me), 1.50 (1H, m), 1.70–2.00 (3H, m), 2.15 (1H, m), 2.22 (1H, d, *J* 5.0, *endo*-methine), 2.71 (1H, m), 2.97 (1H, d, *J* 16.5), 3.27 (1H, septet, *J* 7.0, C*H*Me$_2$), 3.51 (1H, dd, *J* 6.0 and 16.5), 3.77 (1H, t, *J* 5.5, C*H*SO_2Ph), 3.81 (3H, s, OMe), 6.63 (1H, s, Ar-H), 6.71 (1H, s, Ar-H), 7.48 (2H, m, SO_2Ph), 7.62 (3H, m, SO_2Ph); *m*/*z* 451 (M$^+$), 310, 309, 227, 77, 55, 44, 43, 41 and 40 (8.6, 27.9, 100.0, 16.7, 15.3, 15.2, 28.4, 14.8, 18.6 and 94.1%).

The column was flushed with ethanol to give an oil. Chromatography of the oil on silica (140 g) in benzene–ether (47:3) gave in order of elution: 2-(4-isopropyl-5-methoxy-2-methylphenyl)-6,6-dimethyl-8-phenylsulfonylocta-2,7-dienenitrile **9** (Y = CN, X = SO_2Ph) (105 mg, 17%) (Found: C, 71.6; H, 7.1; N, 2.9. $C_{27}H_{33}NO_3S$ requires C, 71.8; H, 7.3; N, 3.1%); ν_{max}(film)/cm^{-1} 2220 and 1620; δ_H(300 MHz) 1.15 (6H, s, 2 × Me), 1.20 (6H, d, *J* 7.0, CH*Me*$_2$), 1.63 (2H, m), 2.31 (3H, s, Ar-*Me*), 2.43 (2H, m), 3.28 (1H, septet, *J* 7.0, C*H*Me$_2$), 3.81 (3H, s, OMe), 6.28 (1H, d, *J* 15.5, olefinic-H), 6.35 (1H, t, *J* 7.5, olefinic-H), 6.63 (1H, s, Ar-H), 6.98 (1H, d, *J* 15.5, olefinic-H), 7.01 (1H, s, Ar-H), 7.56 (3H, m, SO_2Ph), 7.89 (2H, m, SO_2Ph); *m*/*z* 452, 451 (M$^+$), 436, 309, 243, 242, 210, 125, 77 and 41 (37.0, 78.8, 31.4, 27.8, 28.6, 100.0, 25.7, 32.5, 32.1 and 25.3%).

Further elution of the column gave the endo-*chain adduct* **6b** (X = SO_2Ph) (124 mg, 20%) mp 209–210 °C (from ethanol) (Found: M$^+$, 451.2175); ν_{max}(Nujol)/cm^{-1} 2980 and 2220; δ_H (400 MHz, C_6D_6) −0.26 (3H, s, Me), 1.05 (1H, m), 1.10 (2H, m), 1.12 (3H, s, Me), 1.13 (3H, d, *J* 7.0, CH*Me*$_2$), 1.17 (3H, d, *J* 7.0, CH*Me*$_2$), 1.36 (1H, m), 1.77 (1H, td, *J* 14.0 and 4.0), 2.52 (1H, br d, *J* 15.0), 2.71 (1H, dd, *J* 12.0 and 15.0), 3.11 (1H, d, *J* 3.0, *exo*-methine), 3.23 (3H, s, OMe), 3.37 (2H, m, C*H*Me$_2$ and C*H*SO_2Ph), 3.72 (1H, dd, *J* 7.0 and 15.0), 6.54 (1H, s, Ar-H), 6.67 (1H, s, Ar-H), 7.00 (3H, m, SO_2Ph), 7.97 (2H, m, SO_2Ph); *m*/*z* 451 (M$^+$), 310, 309, 227, 225, 184, 77, 55, 43 and 41 (6.7, 37.9, 100.0, 57.0, 24.8, 21.3, 20.1, 16.4, 19.6 and 21.7%).

Further elution of the column gave a dimer of the *o*-quinodimethane intermediate (101 mg, 16%) as an oil (Found: C, 71.6; H, 7.5; N, 2.9; S, 7.2. $C_{54}H_{66}N_2O_6S_2$ requires C, 71.8; H, 7.3; N, 3.1; S, 7.1%); ν_{max}(film)/cm^{-1} 2215 and 2205; δ_H(300 MHz) 1.04 (6H, s), 1.12 (18H, m), 1.44 (7H, m), 2.34 (2H, m, >6 lines), 2.80 (2H, m, >6 lines), 2.92 (2H, d, *J* 6.5), 3.24 (2H, m, C*H*Me$_2$), 3.59 (1H, m, >5 lines), 3.81 (6H, s, OMe), 6.10 (1H, t, *J* 7.5), 6.19 (1H, d, *J* 15.5), 6.28 (1H, d, *J* 15.5), 6.55 (1H, s), 6.76 (1H, s), 6.78 (1H, s), 6.88 (2H, d, *J* 5.5), 6.97 (2H, d, *J* 15.5), 7.60 (6H, m, SO_2Ph), 7.88 (4H, m, SO_2Ph); *m*/*z* 903, 902 (M$^+$), 453, 452, 409, 408, 202, 198, 184 and 125 (31.6, 51.8, 30.6, 88.8, 28.5, 100.0, 25.0, 22.1, 41.5 and 64.6%).

Further elution of the column gave a second dimer of the *o*-quinodimethane intermediate as an oil (64 mg, 5%) (Found: C, 71.7; H, 7.5; N, 2.9; S, 7.0%); ν_{max}(film)/cm^{-1} 2215 and 2205; δ_H(300 MHz) 0.87 (6H, s), 0.97 (6H, s), 1.03 (6H, t, *J* 7.0), 1.12 (6H, t, *J* 7.0), 1.35 (7H, m), 1.65 (1H, m), 1.82 (2H, m), 2.69 (4H, br s), 3.18 (2H, m, C*H*Me$_2$), 3.69 (1H, m), 3.71 (3H, s, OMe), 3.74 (3H, s, OMe), 6.05 (1H, d, *J* 15.5), 6.13 (1H, d, *J* 15.5), 6.44 (1H, s), 6.55 (1H, t, *J* 7.5), 6.70 (1H, s), 6.72 (1H, s), 6.72 (1H, d, *J* 15.5), 6.86 (1H, d, *J* 15.5), 6.91 (1H, s), 7.48 (6H, m, SO_2Ph), 7.79 (4H, m, SO_2Ph); *m*/*z* 903, 902 (M$^+$), 453, 452, 409, 408, 202, 198, 184 and 125 (37.5, 52.5, 42.5, 100.0, 24.4, 66.5, 27.4, 21.6, 41.8 and 54.7%).

By conducting the reaction in dilute solution (0.3 mg ml^{-1}) the formation of dimeric products was avoided and a 67% yield of adducts obtained [40% of **6a** (X = SO_2Ph)].

Alcoholysis of the nitrile 4a (X = SO_2Ph)

Dry hydrogen chloride was bubbled through a solution of **4a** (X = SO_2Ph) (29 mg, 0.064 mmol) in dry methanol (1.5 ml) at 0–5 °C (1 h). The reaction was stirred at this temperature (3 h) and then allowed to warm to 20 °C (14 h). The solution was poured into brine, extracted with ether (×3), washed with water, dried ($MgSO_4$) and concentrated to give an oil. Chromatography on silica (20 g) in benzene–ether (93 : 7) gave methyl 1-(4,4-dimethyl-6-phenylsulfonylhex-5-enyl)-4-isopropyl-5-methoxy-1,2-dihydrobenzocyclobutene-1-carboxylate **11** (26 mg, 84%) (Found: M^+, 484.2271. $C_{28}H_{36}O_5S$ requires M^+, 484.2283); ν_{max}(film)/cm^{-1} 1730; δ_H(300 MHz) 1.05 (6H, s, CMe_2), 1.17 (3H, d, *J* 7.0, CHMe_2), 1.18 (3H, d, *J* 7.0, CHMe_2), 1.34 (4H, m), 1.93 (2H, m), 2.94 (1H, d, *J* 13.5, benzylic-H), 3.32 (1H, septet, *J* 7.0, C*H*Me_2), 3.53 (1H, d, *J* 13.5, benzylic-H), 3.69 (3H, s, CO_2Me), 3.81 (3H, s, OMe), 6.19 (1H, d, *J* 15.5, olefinic-H), 6.72 (1H, s, Ar-H), 6.95 (2H, m, Ar-H and olefinic-H), 7.58 (3H, m, SO_2Ph), 7.87 (2H, m, SO_2Ph); *m*/*z* 485, 484 (M^+), 247, 187, 173, 145, 125, 77, 43 and 41 (38.3, 100.0, 36.8, 25.2, 30.4, 30.1, 33.7, 23.9, 18.4 and 20.2%).

Attempted IMDA addition of 11

The title compound (22 mg, 0.045 mmol) was dissolved in deuterated benzene (0.5 ml) inside an NMR tube and subjected to five freeze–pump–thaw cycles to remove any dissolved oxygen in the system before it was sealed under vacuum. The tube was heated in a thermostatically controlled bath at 160 °C (48 h) and concentrated under reduced pressure to give an oil. Chromatography on silica (28 g) in benzene–ether (24 : 1) gave methyl 2-(4-isopropyl-5-methoxy-2-methylphenyl)-8-phenylsulfonyl-octa-2,7-dienoate **13** (5.4 mg, 24%) (Found: M^+, 484.2286. $C_{22}H_{36}O_5S$ requires M^+, 484.2283); ν_{max}(film)/cm^{-1} 1715; δ_H(300 MHz) 1.13 (6H, s, CMe_2), 1.20 (6H, d, *J* 7.0, CHMe_2), 1.60 (2H, m), 2.10 (3H, s, Ar-*Me*), 2.44 (2H, m), 3.27 (1H, septet, *J* 7.0, C*H*Me_2), 3.71 (3H, s, CO_2Me), 3.81 (3H, s, OMe), 6.01 (1H, t, *J* 7.7, olefinic-H), 6.26 (1H, d, *J* 15.5, olefinic-H), 6.59 (1H, s, Ar-H), 6.96 (1H, s, Ar-H), 7.01 (1H, d, *J* 15.5, olefinic-H), 7.57 (3H, m, SO_2Ph), 7.90 (2H, m, SO_2Ph); *m*/*z* 484 (M^+), 283, 243, 85, 71, 69, 57, 55, 43 and 41 (31.4, 54.0, 69.9, 44.4, 61.5, 47.1, 100.0, 54.5, 82.2 and 56.6%).

Further elution of the column gave the *styrene* **12** (13.2 mg, 60%) (Found: M^+, 484.2285); ν_{max}(film)/cm^{-1} 1710; δ_H(300 MHz) 0.94 (6H, s, CMe_2), 1.20 (6H, d, *J* 7.0, CHMe_2), 1.47 (2H, m), 1.84 (2H, m), 2.02 (3H, s, Ar-*Me*), 3.27 (1H, septet, *J* 7.0, C*H*Me_2), 3.72 (3H, s, CO_2Me), 3.75 (3H, s, OMe), 6.12 (1H, d, *J* 15.5, olefinic-H), 6.42 (1H, s, Ar-H), 6.84 (1H, d, *J* 15.5, olefinic-H), 6.99 (1H, t, *J* 7.5, olefinic-H), 7.02 (1H, s, Ar-H), 7.56 (3H, m, SO_2Ph), 7.80 (2H, m, SO_2Ph); *m*/*z* 484 (M^+), 86, 84, 71, 69, 57, 55, 49, 43 and 41 (100.0, 40.3, 70.0, 60.1, 53.6, 95.2, 56.5, 77.9, 89.8 and 64.1%).

Thermolysis of 4a (X = H)

The benzocyclobutene **4a** (18 mg) was dissolved in *o*-dichlorobenzene (0.5 ml) in an NMR tube and subjected to five freeze–pump–thaw cycles to remove any dissolved oxygen in the system before it was sealed under vacuum. The tube was heated in a thermostatically controlled bath at 180 °C (3 h) and concentrated under reduced pressure to give an oil. Chromatography on silica (28 g) eluting with benzene–petroleum 40–60 °C (3 : 7) gave in order of elution: 1-(4-isopropyl-5-methoxy-2-methylphenyl)-5,5-dimethylhepta-1,6-diene **9** (X = Y = H), (3.2 mg, 18%) (Found: M^+, 311.2250. $C_{21}H_{29}NO$ requires M^+, 311.2249); ν_{max}(film)/cm^{-1} 2920 and 2205; δ_H(400 MHz) 1.20 (12H, m), 1.51 (2H, m), 2.31 (3H, s, Ar-*Me*), 2.48 (2H, m), 3.27 (1H, septet, *J* 7.0, C*H*Me_2), 3.81 (3H, s, OMe), 5.00 (2H, m, olefinic-H), 5.80 (1H, dd, *J* 11.0 and 17.0, olefinic-H), 6.40 (1H, t, *J* 8.0, olefinic-H), 6.62 (1H, s, Ar-H), 7.00 (1H, s, Ar-H); *m*/*z* 311 (M^+), 296, 283, 186, 83, 69, 57, 55, 43 and 41 (56.4, 79.0, 100.0, 64.1, 60.7, 67.7, 81.8, 71.4, 76.9 and 75.1%).

Further elution of the column gave the mixture of *adducts* **6a** and **6b** (X = H) (ratio 1 : 4) (11.8 mg, 66%). The 400 MHz ^1H NMR spectrum was consistent with the published data.

Alkylation of 2 with the iodide 3b

A solution of the benzocyclobutene **2** (300 mg, 1.49 mmol) and sodium hydride (72 mg, 3.0 mmol) in dry distilled DMF (7 ml) was heated at 65 °C (0.5 h). The reaction mixture was cooled to room temperature and a solution of the iodide **3b** (0.44 g, 2.1 mmol) in dry DMF (1.2 ml) was added. The reaction mixture was then heated at 65 °C (1 h), cooled to room temperature, poured into water, diluted with ether and washed with water (×3). The ether layer was dried ($MgSO_4$) and concentrated to give an oil. Chromatography on silica (40 g) eluting with benzene gave the *alkene* **4b** (X = H) as an oil (329 mg, 78%) (Found: C, 80.5; H, 9.1; N, 4.8. $C_{19}H_{25}NO$ requires C, 80.6; H, 8.8; N, 5.0%); ν_{max}(Nujol)/cm^{-1} 2940 and 2230; δ_H(300 MHz) 1.18 (6H, d, *J* 7.0, CHMe_2), 1.48 (2H, m), 1.68 (2H, m), 1.95 (2H, m), 2.11 (2H, m), 3.17 (1H, d, *J* 13.5, benzylic-H), 3.34 (1H, septet, *J* 7.0, C*H*Me_2), 3.63 (1H, d, *J* 13.5, benzylic-H), 3.81 (3H, s, OMe), 4.99 (2H, m, olefinic-H), 5.82 (1H, m, olefinic-H), 6.72 (1H, s, Ar-H), 7.00 (1H, s, Ar-H); *m*/*z* 283 (M^+), 268, 200, 71, 69, 57, 55, 43, 41 and 39 (26.9, 100.0, 43.4, 39.0, 42.2, 71.6, 72.6, 87.2, 92.7 and 34.6%).

Preparation of the aldehyde 8b

To a solution of the alkene **4b** (X = H) (304 mg, 1.07 mmol) and OsO_4 (10 mg) in THF (3.25 ml) and water (1.1 ml) at room temp. was added sodium metaperiodate (493 mg, 2.31 mmol) in portions over 2 h. The reaction mixture was stirred (3 h) then poured into water and extracted with ether (×3), dried ($MgSO_4$) and concentrated to give the crude aldehyde. Chromatography on silica (24 g) eluting with benzene–ether (19 : 1) gave the *aldehyde* **8b** (286 mg, 93%) (Found: C, 75.6; H, 8.3; N, 5.2. $C_{18}H_{23}NO_2$ requires C, 75.8; H, 8.1; N, 4.9%); ν_{max}(Nujol)/cm^{-1} 2940, 2230 and 1725; δ_H(300 MHz) 1.18 (6H, d, *J* 6.5, CHMe_2), 1.71 (4H, m), 1.98 (2H, m), 2.51 (2H, m), 3.18 (1H, d, *J* 13.5, benzylic-H), 3.34 (1H, septet, *J* 6.5, C*H*Me_2), 3.63 (1H, d, *J* 13.5, benzylic-H), 3.81 (3H, s, OMe), 6.72 (1H, s, Ar-H), 7.01 (1H, s, Ar-H), 9.78 (1H, t, *J* 1.5, CHO); *m*/*z* 285 (M^+), 270, 198, 115, 91, 55, 44, 43, 41 and 39 (52.0, 89.7, 50.5, 64.2, 71.1, 50.4, 82.1, 77.5, 100.0 and 86.4%).

Preparation of sulfone 16

To a stirred solution of the foregoing aldehyde (275 mg, 0.96 mmol) in ethanol (15 ml) was added sodium borohydride (55 mg, 1.45 mmol) at 0 °C, and the mixture was allowed to reach room temperature over 1 h. The reaction mixture was poured into water, extracted with ether (×3) and dried ($MgSO_4$). Chromatography of the evaporated product on silica (22 g) eluting with benzene-ether (1 : 1) gave the alcohol (262 mg, 95%), mp 63–64 °C (from dichloromethane–petroleum) (Found: C, 75.5; H, 8.9; N, 4.7. $C_{18}H_{25}NO_2$ requires C, 75.3; H, 8.7; N, 4.9%); ν_{max}(Nujol)/cm^{-1} 3340, 2930 and 2220; δ_H(300 MHz) 1.18 (6H, d, *J* 7.0, CHMe_2), 1.28 (1H, m), 1.48 (2H, m), 1.64 (3H, m), 1.97 (2H, m), 3.18 (1H, d, *J* 13.5, benzylic-H), 3.34 (1H, septet, *J* 7.0, C*H*Me_2), 3.80 (3H, m, benzylic-H and CH_2OH), 3.82 (3H, s, OMe), 6.72 (1H, s, Ar-H), 7.01 (1H, s, Ar-H); the OH signal was not recorded; *m*/*z* 287 (M^+), 273, 272, 216, 215, 214, 200, 199, 198 and 78 (38.4, 20.5, 100.0, 20.2, 16.2, 20.2, 25.6, 12.1, 14.1 and 18.7%).

To a stirred solution of the foregoing alcohol (208 mg, 0.72 mmol) and carbon tetrabromide (300 mg, 0.91 mmol) in dichloromethane (5 ml) was added portionwise triphenylphosphine (285 mg, 1.1 mmol) at 0 °C. The mixture was stirred at 20 °C (1.5 h), poured into water, extracted with CH_2Cl_2 (×3),

dried ($MgSO_4$) and concentrated to give an oil. Chromatography on silica (24 g) eluting with petroleum–benzene (3:7) gave the bromide (233 mg, 92%) (Found: C, 61.9; H, 6.8; N, 4.4. $C_{18}H_{24}BrNO$ requires C, 61.7; H, 6.9; N, 4.0%); ν_{max}(film)/cm^{-1} 2940 and 2220; δ_H(300 MHz) 1.18 (6H, d, *J* 7.0, CH*Me*$_2$), 1.55 (2H, m), 1.72 (2H, m), 1.96 (4H, m), 3.18 (1H, d, *J* 13.5, benzylic-H), 3.34 (1H, septet, *J* 7.0, C*H*Me$_2$), 3.43 (2H, t, *J* 6.5, CH_2Br), 3.64 (1H, d, *J* 13.5, benzylic-H), 3.82 (3H, s, OMe), 6.72 (1H, s, Ar-H), 7.01 (1H, s, Ar-H); *m*/*z* 351, 350 (M^+), 349, 336, 335, 334, 215, 214, 200 and 41 (30.3, 6.8, 30.5, 100.0, 21.2, 98.6, 28.5, 33.9, 33.0 and 27.2%).

To a stirred solution of the foregoing bromide (206 mg, 0.59 mmol) in dry distilled hexamethylphosphoramide (HMPA) (2.5 ml) was added sodium benzenesulfinate (216 mg, 1.31 mmol). The reaction mixture was stirred for 0.5 h at room temperature then poured into water, diluted with ether, washed with water (×3) and dried ($MgSO_4$). Chromatography of the evaporated product on silica (35 g) eluting with benzene–ether (93:7) gave 4-isopropyl-5-methoxy-1-(5-phenylsulfonylpentyl)-1,2-dihydrobenzocyclobutene-1-carbonitrile **16** (210 mg, 87%), mp 142–143 °C (from dichloromethane–ethanol) (Found: C, 69.8; H, 7.0; N, 3.4. $C_{24}H_{29}NO_3S$ requires C, 70.1; H, 7.1; N, 3.4%); ν_{max}(Nujol)/cm^{-1} 2950 and 2230; δ_H(300 MHz) 1.18 (6H, d, *J* 7.0, CH*Me*$_2$), 1.43 (2H, m), 1.62 (2H, m), 1.81 (2H, m), 1.92 (2H, m), 3.12 (3H, m, C*H*$_2$SO$_2$Ph and benzylic-H), 3.34 (1H, septet, *J* 7.0, C*H*Me$_2$), 3.62 (1H, d, *J* 13.5, benzylic-H), 3.82 (3H, s, OMe), 6.69 (1H, s, Ar-H), 7.00 (1H, s, Ar-H), 7.63 (3H, m, SO_2Ph), 7.92 (2H, m, SO_2Ph); *m*/*z* 412, 411 (M^+), 396, 214, 203, 201, 200, 199, 78 and 77 (53.6, 100.0, 66.2, 34.1, 35.0, 47.9, 50.6, 31.5, 83.2 and 64.8%).

Preparation of the alkene 14

To a stirred solution of LDA (2.6 equiv., 0.766 mmol) in THF (2.5 ml) at −78 °C under argon was added a solution of the sulfone **16** (120 mg, 0.29 mmol) in THF (3 ml) rinsing with further THF (1 ml) at −78 °C. The reaction mixture was stirred (15 min) then a solution of diethyl chlorophosphate (61 mg, 3.5 mmol) in THF (1 ml) was added at −78 °C and the reaction mixture was left to reach room temperature over 1 h, when it was poured into dilute HCl (2 mol dm^{-3}), extracted with ether (×3), washed with water and dried ($MgSO_4$) to give the crude phosphonate. The crude product (160 mg, 0.29 mmol) was dissolved in dry THF (3 ml) and cooled to −78 °C under argon and *n*-butyllithium (1.2 equiv. 0.35 mmol) was added. The solution was taken to 0 °C (ice–water bath), paraformaldehyde (56 mg, 0.59 mmol) was added and the mixture was stirred at 0 °C (1 h). The solution was poured into water, extracted with ether (×3) and dried ($MgSO_4$). Chromatography of the evaporated product on silica (28 g) eluting with benzene–ether (19:1) gave 4-isopropyl-5-methoxy-1-(5-phenylsulfonylhex-5-enyl)-1,2-dihydrobenzocyclobutene-1-carbonitrile **14** (91.4 mg, 74%) (Found: C, 70.7; H, 7.0; N, 3.1; S, 7.5. $C_{25}H_{29}NO_3S$ requires C, 70.9; H, 6.9; N, 3.3; S, 7.6%); ν_{max}(film)/cm^{-1} 2940 and 2220; δ_H(300 MHz) 1.18 (6H, d, *J* 7.0, CH*Me*$_2$), 1.60 (4H, m), 1.87 (2H, m), 2.28 (2H, m), 3.12 (1H, d, *J* 13.5, benzylic-H), 3.33 (1H, septet, *J* 7.0, C*H*Me$_2$), 3.60 (1H, d, *J* 13.5, benzylic-H), 3.81 (3H, s, OMe), 5.75 (1H, s, olefinic-H), 6.39 (1H, s, olefinic-H), 6.67 (1H, s, Ar-H), 7.00 (1H, s, Ar-H), 7.59 (3H, m, SO_2Ph), 7.88 (2H, m, SO_2Ph); *m*/*z* 424, 423 (M^+), 408, 242, 214, 200, 199, 198, 78 and 77 (23.0, 75.4, 50.0, 100.0, 26.6, 66.9, 22.0, 21.2, 57.1 and 38.7%).

Attempted IMDA addition of the sulfone 14

The benzocyclobutene **14** (17 mg, 0.04 mmol) was dissolved in deuterated benzene (0.5 ml) in an NMR tube and subjected to five freeze–pump–thaw cycles to remove any dissolved oxygen in the system before it was sealed under vacuum. The tube was heated in a thermostatically controlled bath at 160 °C (16 h). Chromatography of the evaporated product on silica (20 g) eluting with benzene–ether (24:1) gave in order of elution: 7-phenylsulfonyl-1-(4-isopropyl-5-methoxy-2-methylphenyl)octa-2,7-dienenitrile **15** (5.3 mg, 31%) (Found: M^+, 423.1861. $C_{25}H_{29}NO_3S$ requires M^+, 423.1868); ν_{max}(film)/cm^{-1} 2940 and 2220; δ_H(300 MHz) 1.20 (6H, d, *J* 6.5, CH*Me*$_2$), 1.77 (2H, m), 2.29 (3H, s, Ar-*Me*), 2.38 (2H, m), 2.52 (2H, m), 3.28 (1H, septet, *J* 6.5, C*H*Me$_2$), 3.81 (3H, s, OMe), 5.81 (1H, s, olefinic-H), 6.34 (1H, t, *J* 7.5, olefinic-H), 6.42 (1H, s, olefinic-H), 6.62 (1H, s, Ar-H), 7.01 (1H, s, Ar-H), 7.59 (3H, m, SO_2Ph), 7.90 (2H, m, SO_2Ph); *m*/*z* 423 (M^+), 200, 149, 77, 71, 69, 57, 55, 43 and 41 (100.0, 65.1, 69.7, 65.8, 52.1, 44.3, 86.8, 53.3, 91.3 and 59.6%).

Further elution of the column gave a dimer of the *o*-quinodimethane intermediate (8.8 mg, 52%); ν_{max}(film)/$^{-1}$ 2240 and 2220; δ_H(400 MHz) 1.20 (12H, m), 1.44 (4H, m), 1.72 (4H, m), 2.20 (2H, m, >5 lines), 2.33 (2H, t, *J* 8.0), 2.44 (2H, m, >8 lines), 2.75 (2H, m), 2.89 (2H, t, *J* 7.5), 3.25 (2H, m, C*H*Me$_2$), 3.60 (1H, dd, *J* 9.5 and 4.5), 3.80 (6H, s, OMe), 5.69 (1H, s), 5.79 (1H, s), 6.13 (1H, t, *J* 7.5), 6.34 (1H, s), 6.39 (1H, s), 6.54 (1H, s), 6.76 (2H, d, *J* 12.5), 6.88 (1H, s), 7.58 (6H, m, SO_2Ph), 7.85 (4H, m, SO_2Ph); *m*/*z* 846 (M^+), 424, 380, 125, 78, 77, 71, 69, 57 and 43 (59.0, 100.0, 80.0, 41.7, 38.8, 46.1, 48.7, 41.8, 64.6 and 59.1%).

Desulfurisation of the adduct 6a (X = SO_2Ph)

A solution of the adduct (132 mg, 0.29 mmol) in DBU (20 ml) was heated at a bath temperature of 130 °C (3 h). The solution was diluted with ether, washed with dilute HCl then water, dried ($MgSO_4$) and concentrated to give 7-isopropyl-6-methoxy-1,1-dimethyl-1,2,3,4,4a,10a-hexahydrophenanthrene-4a-carbonitrile **18**. Chromatography on silica (20 g) eluting with benzene–petroleum gave the *olefin* **18** (83 mg, 92%), mp 157.5–158.0 °C (from dichloromethane–ethanol) (Found: M^+, 309.2105. $C_{21}H_{27}NO$ requires *M*, 309.2093); ν_{max}(Nujol)/cm^{-1} 2220 and 1610; δ_H(400 MHz) 1.03 (3H, s, Me), 1.19 (3H, d, *J* 7.0, CH*Me*), 1.21 (3H, d, *J* 7.0, CH*Me*), 1.28 (3H, s, Me), 1.58 (1H, m), 1.63 (1H, m), 1.75 (1H, dt, *J* 13.5 and 3.5), 1.86 (1H, dq, *J* 14.0 and 3.5), 2.01 (1H, tt, *J* 14.0 and 3.5), 2.09 (1H, t, *J* 3.0, *endo*-methine), 2.73 (1H, m), 3.28 (1H, septet, *J* 7.0, C*H*Me$_2$), 3.85 (3H, s, OMe), 6.00 (1H, dd, *J* 2.5 and 10.0, olefinic-H), 6.66 (1H, dd, *J* 3.0 and 10.0, olefinic-H), 6.80 (1H, s, Ar-H), 7.01 (1H, s, Ar-H); *m*/*z* 310, 309 (M^+), 294, 227, 225, 210, 56, 55, 43 and 41 (24.9, 100.0, 30.3, 45.5, 27.9, 32.7, 18.4, 14.4, 17.5 and 23.4%).

Hydrogenation of the olefin 18

A solution of the title compound (72 mg, 0.23 mmol) in dry distilled ethyl acetate (5.5 ml) was hydrogenated in the presence of 10% Pd on activated charcoal (15 mg) for 2 h. The solution was filtered through Celite and concentrated to give the *nitrile* **6a** (X = H) (72 mg, 98%), mp 154.0–154.5 °C (from dichloromethane–ethanol) (Found: C, 80.8; H, 9.5; N, 4.5. $C_{21}H_{29}NO$ requires C, 81.0; H, 9.3; N, 4.5%); ν_{max}(film)/cm^{-1} 2220; δ_H(400 MHz) 1.01 (3H, s, Me), 1.16 (3H, s, Me), 1.18 (3H, d, *J* 7.0, CH*Me*$_2$), 1.19 (3H, d, *J* 7.0 CH*Me*$_2$), 1.26 (1H, td, *J* 14.0 and 3.5), 1.37 (1H, dd, *J* 12.0 and 2.0, *endo*-methine), 1.52 (1H, td, *J* 13.5 and 3.5), 1.59 (1H, m), 1.83 (2H, m, C*H*$_2$CH masked by ring C CH_2), 2.04 (2H, m, CH_2CH masked by ring C CH_2), 2.80 (2H, m, benzylic-H masked by ring C CH_2), 2.94 (1H, ddd, *J* 16.5, 6.0 and 1.5, benzylic-H), 3.24 (1H, septet, *J* 7.0, C*H*Me$_2$), 3.81 (3H, s, OMe), 6.83 (1H, s, Ar-H), 6.92 (1H, s, Ar-H); *m*/*z* 312, 311 (M^+), 297, 296, 284, 176, 163, 161, 147 and 117 (25.1, 77.9, 34.3, 100.0, 8.2, 5.9, 6.0, 7.1, 6.4 and 5.7%).

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