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The synthesis and electronic absorption spectra of 3-phenyl-3(4-pyrrolidino-2-substituted phenyl)-3*H*-naphtho[2,1-*b*]pyrans: further exploration of the *ortho* substituent effect

Christopher D. Gabbutt, B. Mark Heron* and Alicia C. Instone

Department of Colour and Polymer Chemistry, The University of Leeds, Leeds LS2 9JT, UK

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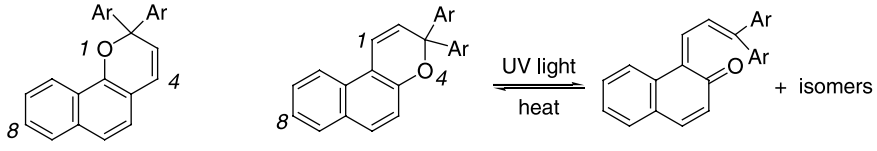
Abstract—Introduction of a substituent into a sterically demanding 2-position of a 3-(4-pyrrolidinophenyl) ring of a 3,3-diaryl-3*H*-naphtho[2,1-*b*]pyran results in the generation of an additional short wavelength absorption band leading to organic photochromes that appear as dull shades of orange and red.

1. Introduction

The electrocyclic ring-opening–ring-closing sequence of the isomeric diaryl substituted naphthopyrans **1** and **2** (Scheme 1) with the accompanying colour change has rendered these compounds invaluable to the ophthalmic photochromic sun and contact lens industries.[1] Other applications of photochromic naphthopyrans, for example, in fuel[2] and security markers,[3] as UV light intensity indicators[4] and as hair dyes[5] have been documented.

Optimising the photochromic response of these T-type[6] naphthopyrans has attracted significant academic[7] and industrial attention.[1] Perhaps the simplest and most significant means to achieve control of the hue and persistence of the ring-opened isomer of the naphthopyran system is through the manipulation of substituents located on the geminal diaryl unit.[8] The intensification of the photo-generated colour of **2** has been accomplished through the introduction of a group into at least one of the *ortho* positions of one of the aryl groups attached to 3-C, for example, **3**.[9] This phenomenon has been attributed to a steric effect in which the *ortho* substituent hinders the thermal ring closure of the photo-generated coloured species to the colourless pyran form; a feature that has recently been correlated to the size of the introduced group in **4**.[10] The net result of this steric effect is a photostationary state in which there is an appreciable concentration of the ring-opened form, which is manifest in an intensification of the developed colour. Further manipulation of the photochromism of naphthopyrans has been accomplished through steric interactions between a terminal pyrrolidine donor function and neighbouring substituents, for example, **5**. In this instance, as the magnitude of these steric interactions increase λ_{max} is shifted hypsochromically until a maximum interaction is observed with **5**, X=Br.[11]



1
2*H*-naphtho[1,2-*b*]pyran

2
3*H*-naphtho[2,1-*b*]pyran

Scheme 1.

Keywords: Naphthopyrans; Photochromism; Steric effects; Dual absorption bands; Synthesis.
* Corresponding author. Tel.: +44 113 3432925; fax: +44 113 3432947; e-mail: b.m.heron@leeds.ac.uk

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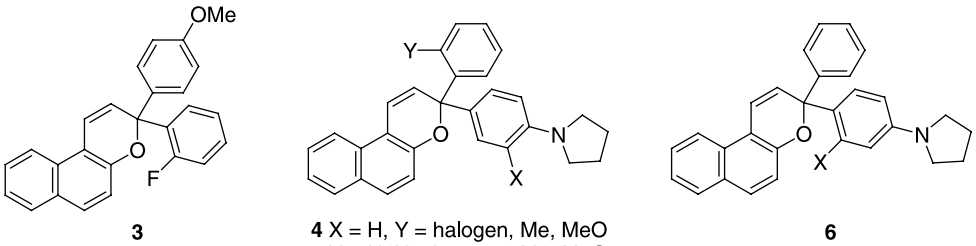


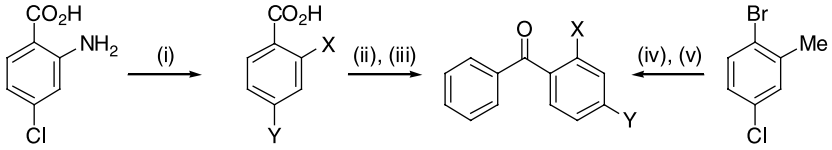
3 **4** X = H, Y = halogen, Me, MeO; **5** Y = H, X = halogen, Me, MeO **6**

We were interested in exploring novel naphthopyrans of type **6** in which the influence of alternating the nature of X, located in a sterically demanding position in the main electron donating aryl moiety, upon the photochromic response could be investigated.[12]

2. Results and discussion

In order to synthesise **6** we required access to a range of 2-substituted 4-pyrrolidinobenzophenones. Thus, the dihalogenobenzoic acids **7a**,**b** were accessed by diazonium salt chemistry from 4-chloroanthranilic acid.[13] Conversion to the acid chlorides and a subsequent Friedel-Crafts reaction with benzene afforded the benzophenones **8a**,**b** (Scheme 2). 2-Chloro-4-fluorobenzophenone **8c** was obtained in a similar manner from 2-chloro-4-fluorobenzoic acid. Using this Friedel-Crafts protocol with 4-chloro-2-methoxybenzoic acid resulted in concomitant demethylation and benzoylation[14] to give 4-chloro-2-hydroxybenzophenone **8e**. *O*-Methylation of **8e** was only accomplished in low yield using excess MeI and powdered KOH in DMSO to afford the 2-methoxybenzophenone **8f**. 4-Chloro-2-methybenzophenone was accessed in 76% yield by the action of the Grignard reagent derived from 2-bromo-5-chlorotoluene on the Weinreb amide,[11,15] *N*-methoxy-*N*-methylbenzamide.

We have previously employed the nucleophilic substitution of an activated halogen atom from benzophenones to afford aminosubstituted benzophenones.[11,16] However, the present benzophenones, **8a–d**, contain two halogen atoms that are activated towards nucleophilic displacement. Heating **8d** in an excess of pyrrolidine resulted in the formation of 2,4-dipyrrolidinobenzophenone **9** (72%) and 4-fluoro-2-pyrrolidinobenzophenone **10a** (17%) which were separated by column chromatography. None of the desired benzophenone **11d** was isolated from the crude product. It is likely that the initial reaction involves preferential displacement of the 4-fluorine atom of **8d** to afford 2-fluoro-4-pyrrolidinobenzophenone **11d** together with a smaller amount of **10a** as a consequence of the simultaneous but less favoured displacement of the 2-fluorine atom. However, under prolonged heating, the 2-fluorine atom of **11d**, although electronically deactivated towards displacement due to the 4-pyrrolidine substituent diminishing the electron withdrawing influence of the C=O group, is still sufficiently activated towards displacement leading to **9**. Displacement of the 4-fluorine atom from **10a** is less likely since the steric interaction between the 2-pyrrolidine unit and the C=O group result in rotation of the C=O unit out of conjugation with the fluorophenyl ring, which renders the F atom inactive towards displacement. A modified version of this protocol was next investigated in which 1 equiv of pyrrolidine was employed with added K_2CO_3 base (Method 1). Termination of the reaction after ~1 h gave a product from which **10a** (28%) and the desired **11d** (37%) were isolated by column chromatography. Repeating this protocol with benzophenones **8a–c** provided access to the desired 2-substituted 4-pyrrolidinobenzophenones though in each case their formation was accompanied by varying amounts of the 2-pyrrolidino substituted benzophenone **10a** or **10b** and **9** (Scheme 3). The conversion of benzophenones **8f**,**g** to **11f**,**g**, respectively, was particularly sluggish requiring 4 days heating in the presence of DMSO to effect even a mediocre yield of the products (Method 2). Interestingly the formation of **11f** was accompanied by some of the demethylated compound **11e** (19%).



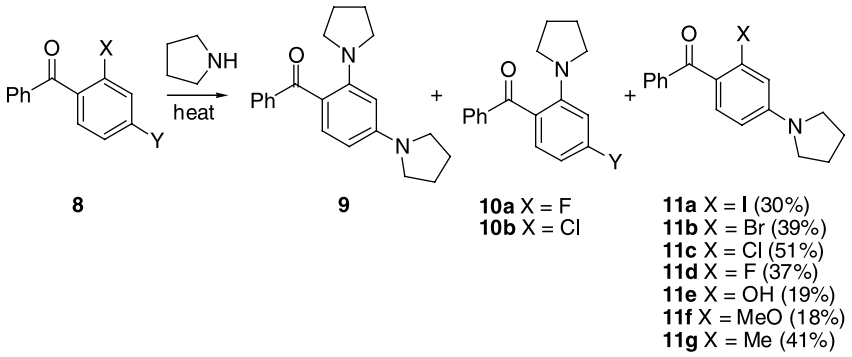
7a X = I, Y = Cl (60%)
7b X = Br, Y = Cl (61%)
7c X = Cl, Y = F
7d X = MeO, Y = Cl

8a X = I, Y = Cl (66%)
8b X = Br, Y = Cl (70%)
8c X = Cl, Y = F (99%)
8d X = Y = F
8e X = OH, Y = Cl (81%)
8f X = MeO, Y = Cl (25%)
8g X = Me, Y = Cl (76%)

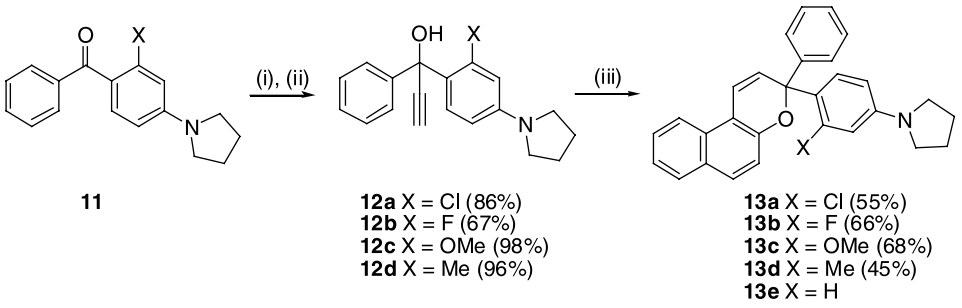
(vi)

Reagents: (i) c.HCl, $NaNO_2$, H_2O, 0 °C then either CuBr or KI and heat; (ii) $SOCl_2$, heat; (iii) $AlCl_3$, PhH, heat; (iv) Mg, anhyd. Et_2O, heat; (v) *N*-methoxy-*N*-methylbenzamide, anhyd. Et_2O, heat then aq. HCl; (vi) excess MeI, KOH, DMSO, 40 °C

Scheme 2.



Scheme 3.



Scheme 4.

The majority of the benzophenones **11** were efficiently transformed into the prop-2-yn-1-ols **12a–d** on reaction with an excess of lithium trimethylsilylacetylide, which was derived from *n*-butyllithium and trimethylsilylacetylene. Removal of the TMS group from the initial adduct was accomplished in the same flask by addition of methanolic KOH (2 equiv). Yields for this conversion were typically high (67–98%) (Scheme 4).[10,11,17] Somewhat surprisingly the reaction of both **11a** and **11b** failed to give any of the propynols and instead multicomponent mixtures were formed. Attempts to isolate the trimethylsilyl intermediates were also unsuccessful.

The most versatile and efficient route to 3,3-diaryl-3*H*-naphtho[2,1-*b*]pyrans relies upon the one pot, acid-catalysed reaction of a 2-naphthol with a 1,1-diarylprop-2-yn-1-ol; a transformation that was developed from an original naphthopyran synthesis reported by Iwae and Ide in 1962.[18] Heating the propynols **12** with 2-naphthol in toluene in the presence of acidic alumina gave the naphthopyrans **13a–d** in 45–68% yield (Scheme 4).

The ^{1}H NMR spectra of **13a**,**c**,**d** displayed a doublet at $\sim\delta$ 6.3 with a coupling constant of 10 Hz characteristic of 2-H in 3*H*-naphtho[2,1-*b*]pyrans.[11,17,19] The doublet for 1-H was obscured by the aromatic protons, however, 2D ^{1}H–^{1}H COSY experiments revealed that 3-H resonated at $\sim\delta$ 7.3. The fluorine substituted compound **13b**, afforded a double doublet at δ 6.30 for 2-H with $J=10.0$, 3.6 Hz (Fig. 1).

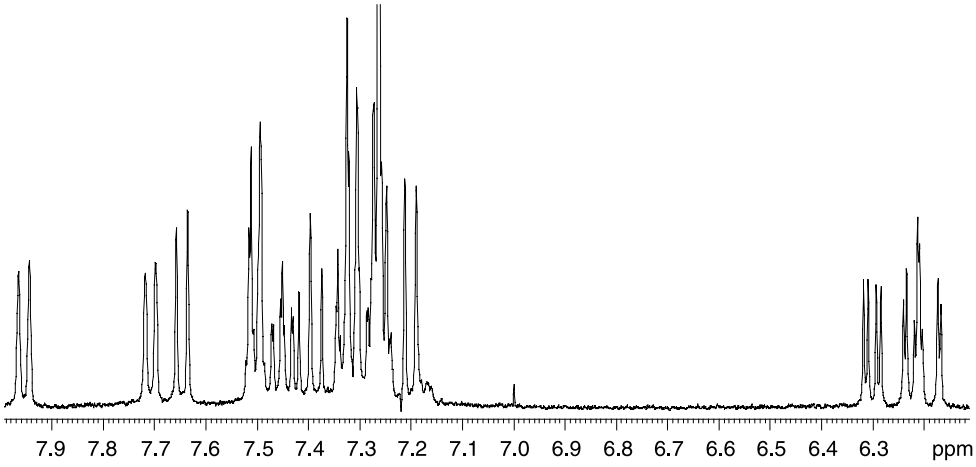
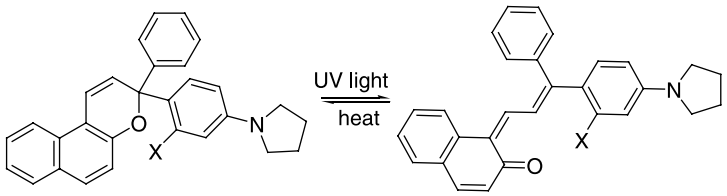


Figure 1. ^{1}H NMR spectrum (6–8 ppm) of Naphthopyran **13b**.

Table 1. Spectroscopic data for naphthopyrans **13**



13

Entry	X	λ_{max} (nm)		$t_{½}$ (s)
13a	Cl	403	480	44
13b	F	394	501	21
13c	OMe	399	519	73
13d	Me	410	507	104
13e	H	538		5

This additional coupling is due to long range coupling of the proximal fluorine atom to 2-H.[10]

The spectroscopic data (Table 1) and selected spectra (Fig. 2) obtained for toluene solutions of the naphthopyrans (**13a**–**e**) merit some comment. The most striking feature of these spectra is the appearance of two absorption maxima of approximately equal intensity (for **13a**,**d**) in the visible region; a short wavelength band at ca. 400 nm and the expected longer wavelength band at ca. 500 nm. This feature is most unusual and to our knowledge provides the first example of an unsymmetrically substituted 3*H*-naphtho[2,1-*b*]pyran displaying such absorption characteristics.[20] Symmetrical 3,3-bis(4-dialkylaminophenyl)-3*H*-naphtho[2,1-*b*]pyrans, for example, 3,3-bis(4-dimethylaminophenyl)-3*H*-naphtho[2,1-*b*]pyran (λ_{max} 446 and 560 nm in PhMe solution), exhibit two absorption bands in the visible region but typically, the short wavelength band is present as a much less intense band or shoulder.[21] Additionally, the overall lifetime of the photo-generated species derived from these symmetrically substituted compounds is very short with $t_{½}$ typically less than 1 s, which renders these compounds ineffective as materials for ophthalmic lens applications.

If we first consider the data for **13b** X=F, and compare this with the data for the parent compound **13e** X=H, which displays a single absorption band with λ_{max} 538 nm ($t_{½}$ = 5 s) it can be seen that the incorporation of the *ortho* X group has induced a hypsochromic shift in λ_{max} of the long wavelength band. This shift in λ_{max} is due to the twisting of the pyrrolidinophenyl unit out of plane with the remainder of the conjugated system and hence reducing the donor properties of this unit as a result of less efficient π overlap, which leads to the observed hypsochromic shift. One further consequence of the pyrrolidinophenyl unit twisting is that the remaining phenyl ring may now adopt a more planar arrangement thus increasing its donor potential, which we believe results in a bathochromic shift and intensification of a band from the UV region into the yellow end of the visible spectrum at 394 nm. The larger chlorine atom in compound **13a** results in the pyrrolidinophenyl unit twisting further out of plane, which leads to a greater hypsochromic shift in the long wavelength band of 21 nm compared to **13b**, and a

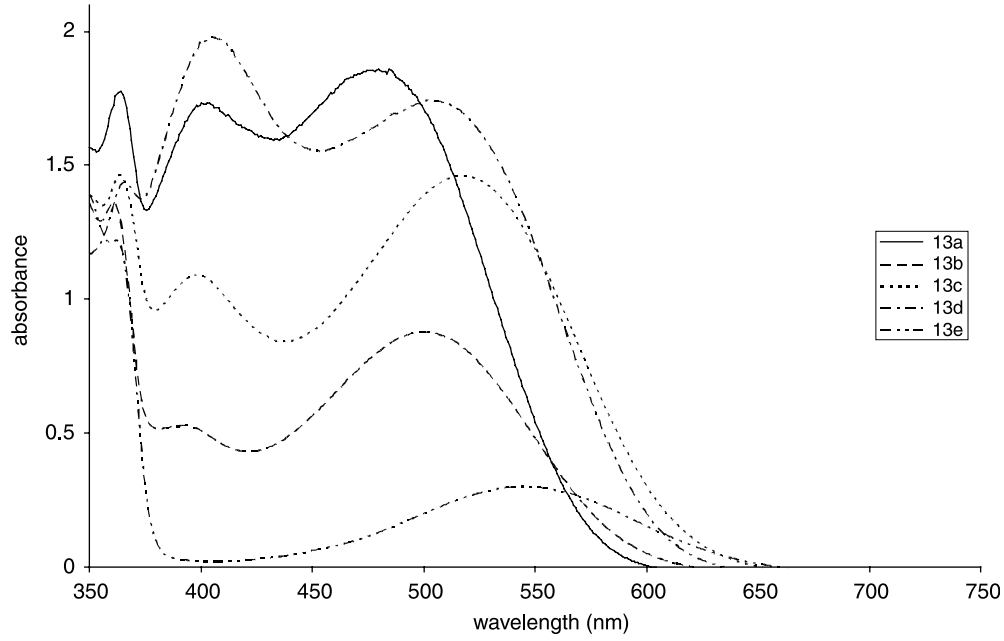


Figure 2. UV–visible spectra for toluene solutions of Naphthopyrans **13** after UV irradiation.

10 nm bathochromic shift in the shorter wavelength band to 403 nm relative to that of **13b**.

It is immediately apparent that the spectroscopic data for the methoxy **13c** and methyl **13d** substituted naphthopyrans are at odds with the trend suggested for **13a** and **13b**. Available data[10,11,22] would suggest that a methyl group is similar in its spatial requirements to a chlorine atom but has markedly different electronic properties. It may be that for **13d** the effect of the reduced conjugation induced by twisting is countered by the donor properties of the methyl group leading to a bathochromic shift in λ_{max} to 507 nm. However, this inductive electron donation cannot easily be aligned with the accompanying bathochromic shift in the short wavelength band to 410 nm. The long wavelength band for **13c** appears at 519 nm, which would support the influence of the *ortho* donor group increasing conjugation, however, the short wavelength band appears at 399 nm midway for the series of **13**. Clearly there is some subtle interplay between the two aryl rings of the naphthopyrans **13c** and **13d**, which bear electron donating *ortho* substituents.

The half-life data presented in Table 1 of the coloured ring-opened forms relates to the time taken for the intensity of the long wavelength absorption band under steady state conditions to fade to half its original value upon cessation of irradiation. The half-life of **13b** is 21 s, which is in accord with our earlier results since fluorine is the smallest group and thus induces less steric hindrance during the ring-closing process.[10] As expected the chloro compound **13a** has a longer half-life of 44 s, due to the increased steric effects associated with its larger size. The methyl compound **13d** has an unusually long half-life, 104 s, compared to that of the chloro compound, even though it is of a similar size.[22] The methoxy compound **13c** with a half-life of 73 s, falls between that determined for **13d** and **13b** and is in agreement with data for previous comparisons between the *o*-tolyl and *o*-methoxyphenyl C-3 substituted naphthopyrans.[10]

In summary, the introduction of a group into one of the C-3 aryl groups *ortho* to the point of attachment of the group to the pyran ring and *meta* to a strong electron donor group induces a dramatic change in the appearance of the visible spectrum of the photo-generated dye from a single absorption band to two bands of approximately equal intensity when the *ortho* group is spatially demanding (**13**, X=Cl, Me). The appearance of the spectrum has been rationalised by considering steric interactions between the two aryl rings and the remainder of the chromophore. The ability to manipulate the appearance of the visible spectrum may be of value in the design of new neutral shades of naphthopyrans, which presently rely upon either amino substituted 2*H*-naphtho[1,2-*b*]pyrans[23] or heterocyclic fused benzo- and naphtho- pyrans.[24]

3. Experimental

3.1. General

Melting points were determined in capillary tubes and are uncorrected. Visible spectra were recorded for ca. 3×10^{-5} mol dm^{-3} solutions in spectroscopic grade toluene in 10 mm quartz cells at 21 °C using an Analytik Jena Specord S100 diode array spectrophotometer. Samples were irradiated to a steady state of absorbance using a Spectroline 8 W lamp (365 nm). Infrared spectra were recorded on a Perkin-Elmer 882 spectrophotometer in KBr discs unless otherwise specified. NMR spectra were recorded on a Bruker Avance 400 MHz instrument for solutions in $CDCl_3$; *J* values are given in Hz. Flash chromatography separations were performed on chromatography silica (40–60 μm particle size distribution) as supplied by Fluorochem Ltd.

3.2. Preparation of 2-substituted-4-chlorobenzoic acids

A solution sodium nitrite (7.05 g, 102 mmol) in water (15 mL) was added slowly to a cold (0 °C) stirred solution of 2-amino-4-chlorobenzoic acid (17.16 g, 100 mmol) in water (250 mL) and concd HCl (75 mL). On completion of the addition the solution was stirred for 5 min and then a solution of the appropriate halide (102 mmol) in water (25 mL) was added. The cooling bath was removed and the mixture stirred for a further 5 min before carefully heating the suspension to 90 °C for 10 min. The mixture was cooled to room temperature and the precipitated solid collected and washed with water (3×50 mL). The crude product was recrystallised from ethanol and water. The following acids were prepared in this way:

3.2.1. 4-Chloro-2-iodobenzoic acid 7a. From potassium iodide as a light brown powder (16.9 g, 60%), mp 160–163 °C (lit. mp 165–166 °C[25]), δ_H 3.49 (1H, br s, OH), 7.63 (1H, dd, *J*=8.4, 2.1 Hz, 5-H), 7.80 (1H, d, *J*=8.3 Hz, 6-H), 8.14 (1H, d, *J*=2.1 Hz, 3-H).

3.2.2. 2-Bromo-4-chlorobenzoic acid 7b. From copper(I) bromide as a light brown powder (14.4 g, 61%), mp 154–156 °C (lit. mp 155 °C[26]), δ_H 3.84 (1H, br s, OH), 7.46 (1H, dd, *J*=8.3, 2.1 Hz, 5-H), 7.65 (1H, d, *J*=2.0 Hz, 3-H), 7.76 (1H, d, *J*=8.4 Hz, 6-H).

3.3. Preparation of 2-substituted-4-halogeno-benzophenones

The 2-substituted-4-halogenobenzoic acid **7** (26 mmol), thionyl chloride (4.40 mL, 60 mmol) and one drop of *N*,*N*-dimethylformamide were heated under reflux for 2 h. The excess thionyl chloride was removed from the cooled reaction mixture and the remaining acid chloride was dissolved in benzene (116 mL, 1.3 mol). Aluminium chloride (3.87 g, 29 mmol) was added portion-wise over ca. 10 min to this solution and the resulting suspension was refluxed for ca. 1 h. The reaction mixture was poured onto ice (300 g) and concd HCl (50 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3×100 mL). The combined organic phases were washed with 5% aqueous NaOH solution (50 mL), water (3×50 mL) and dried (anhyd Na_2SO_4). Removal of the solvent gave the crude benzophenones that were recrystallised from hexane and ethyl acetate. The following benzophenones were obtained by this protocol:

3.3.1. 4-Chloro-2-iodobenzophenone 8a. From 4-chloro-2-iodobenzoic acid as pale brown microcrystals (5.9 g,

66%), mp 60–62 °C, ν_{max} 1676, 1594, 1572 cm^{-1}, δ_H 7.23 (1H, d, J=8.3 Hz, 6-H), 7.42 (1H, dd, J=8.2, 2.0 Hz, 5-H), 7.48 (2H, m, 3′,5′-H), 7.62 (1H, m, 4′-H), 7.78 (2H, m, 2′,6′-H), 7.94 (1H, d, J=1.9 Hz, 3-H). (Found: C, 45.6; H, 2.2; $C_{13}H_8ClIO$ requires C, 45.6; H, 2.4%).

3.3.2. 2-Bromo-4-chlorobenzophenone 8b. From 2-bromo-4-chlorobenzoic acid as a colourless viscous oil (5.4 g, 70%), bp 155 °C at 0.4 mmHg (lit. bp 220 °C at 14 mmHg[26]), δ_H 7.33 (1H, m, Ar-H), 7.46 (4H, m, Ar-H), 7.59 (1H, m, Ar-H), 7.78 (2H, m, Ar-H).

3.3.3. 2-Chloro-4-fluorobenzophenone 8c. From 2-chloro-4-fluorobenzoic acid as colourless microcrystals (6.0 g, 99%), mp 40–42 °C (lit. mp 45–47 °C[27]), δ_H 7.09 (1H, m, 5-H), 7.21 (1H, dd, J=8.5, 2.4 Hz, 3-H), 7.40 (1H, dd, J=8.5, 5.9 Hz, 6-H), 7.47 (2H, m, 3′,5′-H), 7.60 (1H, m, 4′-H), 7.79 (2H, m, 2′,6′-H).

3.3.4. 4-Chloro-2-hydroxybenzophenone 8e. From 4-chloro-2-methoxybenzoic acid as cream microcrystals (4.9 g, 81%), mp 70–71 °C (lit. mp 74.5 °C[28]), δ_H 6.86 (1H, dd, J=8.6, 2.0 Hz, 5-H), 7.10 (1H, d, J=2.0 Hz, 3-H), 7.53 (3H, m, 6-H, 3′,5′-H), 7.61 (1H, m, 4′-H), 7.66 (2H, m, 2′,6′-H), 12.20 (1H, s, OH).

3.4. Preparation of 4-chloro-2-methoxybenzophenone

Methyl iodide (4.66 mL, 74.8 mmol) was added to a stirred solution of 4-chloro-2-hydroxybenzophenone **8e** (8.70 g, 37.4 mmol) and finely ground potassium hydroxide (2.30 g, 41.1 mmol) in anhyd dimethylsulfoxide (40 mL). The mixture was maintained at 40 °C and after 4 h further methyl iodine (4.66 mL, 74.8 mmol) was added to the mixture. After heating for 14 h at 40 °C a further quantity of methyl iodide (4.66 mL, 74.8 mmol) was added and the mixture stirred at 40 °C for a further 3 h. The solution was poured into water (300 mL), the organic layer was separated and the aqueous layer extracted with ethyl acetate (3× 100 mL). The organic phases were combined, washed with brine (5×50 mL), water (100 mL), dried (anhyd Na_2SO_4) and evaporated. The title compound **8f** was obtained after column chromatography using 10% ethyl acetate in hexane as colourless microcrystals (2.3 g, 25%), mp 91–93 °C, ν_{max} 1651, 1588, 1567 cm^{-1}, δ_H 3.72 (3H, s, OCH_3), 6.98 (1H, d, J=1.7 Hz, 3-H), 7.04 (1H, dd, J=8.1, 1.8 Hz, 5-H), 7.31 (1H, d, J=8.1 Hz, 6-H), 7.43 (2H, m, 3′,5′-H), 7.56 (1H, m, 4′-H), 7.78 (2H, m, 2′,6′-H), δ_C 56.3, 112.6, 121.1, 127.6, 128.7, 130.2, 131.1, 133.6, 137.9, 138.0, 158.5, 195.7. (Found: C, 67.9; H, 4.5; $C_{14}H_{11}ClO_2$ requires C, 68.2; H, 4.5%).

3.5. Preparation of 4-chloro-2-methylbenzophenone

A solution of 2-bromo-5-chlorotoluene (13.3 mL, 100 mmol) in anhyd diethyl ether (40 mL) was added drop wise to magnesium turnings (2.55 g, 105 mmol) in anhyd diethyl ether (40 mL). After ca. ⅓ of the solution of 4-bromo-2-chloroanisole had been added one crystal of iodine was added and the mixture stirred. Upon initiation of the reaction mixture the remaining solution of 2-bromo-5-chlorotoluene was added at such a rate so as to maintain a steady reflux. On completion of the addition the suspension was refluxed for a further 1 h and then cooled to room temperature. A solution of *N*-methoxy-*N*-methylbenzamide (10.2 mL, 67 mmol) in anhyd diethyl ether (20 mL) was added drop wise via syringe to this solution of the Grignard reagent so as to maintain a constant reflux. On completion of the addition the mixture was refluxed for a further 2 h and then left to stand overnight at room temperature. The mixture was poured onto ice (~200 g) and aqueous HCl (100 mL, 2 M) and the organic layers separated. The aqueous layer was extracted with ethyl acetate (3× 100 mL) and the combined organic phases were washed with water (3×50 mL), dried (anhyd Na_2SO_4) and evaporated to afford the crude product. Elution from silica using 40% ethyl acetate in hexane as the eluent gave 4-chloro-2-methylbenzophenone **8g** as a yellow oil (11.7 g, 76%) bp 135 °C at 0.4 mmHg (lit. bp 150–155 °C at 0.5 mmHg[29]), δ_H 2.32 (3H, s, CH_3), 7.25 (3H, m, Ar-H), 7.46 (2H, m, 3′, 5′-H), 7.59 (1H, m, 4′-H), 7.77 (2H, m, 2′, 6′-H).

3.6. Attempted preparation of 2-fluoro-4-pyrrolidinobenzophenone

2,4-Difluorobenzophenone **8d** (5.02 g, 23 mmol) was dissolved in pyrrolidine (11.7 mL, 140 mmol) and stirred at room temperature for 10 min and then heated under reflux until TLC examination of the reaction mixture indicated that no further changes were apparent (~5 h). The cooled mixture was poured into water (300 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined organic phases were washed with water (6×50 mL), dried (anhyd Na_2SO_4) and evaporated to afford the crude product. Purification was effected by elution from silica with 30% EtOAc in hexane to afford two fractions

Fraction 1. 4-Fluoro-2-pyrrolidinobenzophenone **10a** as yellow microcrystals (1.05 g, 17%), mp 74–75 °C, ν_{max} 1646, 1614, 1577 cm^{-1}, δ_H 1.91 (4H, m, $(CH_2)_2$), 3.12 (4H, m, $N(CH_2)_2$), 6.37 (1H, m, 5-H), 6.50 (1H, dd, J=12.8, 2.4 Hz, 3-H), 7.24 (1H, m, 6-H), 7.47 (2H, m, 5′,3′-H), 7.57 (1H, m, 4′-H), 7.91 (2H, m, 2′,6′-H). (Found: C, 76.0; H, 6.1; N, 5.2; $C_{17}H_{16}NOF$ requires C, 75.8; H, 6.0; N, 5.2%).

Fraction 2. 2,4-Dipyrrolidinobenzophenone **9** as yellow microcrystals (5.3 g, 72%), mp 142–145 °C, ν_{max} 1624, 1602, 1575 cm^{-1}, δ_H 1.89 (4H, m, $(CH_2)_2$), 2.01 (4H, m, $(CH_2)_2$), 3.21 (4H, m, $N(CH_2)_2$), 3.35 (4H, m, $N(CH_2)_2$), 5.85 (1H, d, J=2.0 Hz, 3-H), 5.93 (1H, dd, J=8.7, 2.1 Hz, 5-H), 7.24 (1H, d, J=8.6 Hz, 6-H), 7.42 (2H, m, 5′,3′-H), 7.49 (1H, m, 4′-H), 7.87 (1H, m, 2′,6′-H). (Found: C, 78.9; H, 7.7; N, 8.7; $C_{21}H_{24}N_2O$ requires C, 78.7; H, 7.6; N, 8.7%).

3.7. Preparation of 2-substituted 4-pyrrolidinobenzophenones (Method 1)

The halogenobenzophenone **8** (23 mmol) was dissolved in pyrrolidine (1.92 mL, 23 mmol) containing potassium carbonate (0.32 g, 23 mmol) and stirred at room temperature for 10 min and then heated under reflux until TLC examination of the reaction mixture indicated that formation of 2,4-dipyrrolidinobenzophenone commenced (~1 h).

The cooled mixture was poured into water (100 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined organic phases were washed with water (6×50 mL), dried (anhyd Na_2SO_4) and evaporated to afford the crude product. Purification was effected by elution from silica with 30% EtOAc in hexane. The following benzophenones were prepared in this manner:

3.7.1. 2-Iodo-4-pyrrolidinobenzophenone 11a. From 4-chloro-2-iodobenzophenone **8a**, elution from silica gave three fractions. *Fraction 1*. 2-Iodo-4-pyrrolidinobenzophenone **11a** as yellow microcrystals (2.60 g, 30%), mp 117–120 °C, ν_{max} 1642, 1593 cm^{-1}, δ_H 1.90 (4H, m, $(CH_2)_2$), 3.12 (4H, m, $N(CH_2)_2$), 6.64 (1H, dd, J=8.3, 1.9 Hz, 5-H), 6.81 (1H, d, J=1.9 Hz, 3-H), 7.17 (1H, d, J=8.3 Hz, 6-H), 7.47 (2H, m, 3′,5′-H), 7.56 (1H, m, 4′-H), 7.91 (2H, m, 2′,6′-H), δ_C 26.3, 51.7, 114.1, 115.1, 122.8, 128.8, 130.8, 133.0, 133.2, 137.9, 138.5, 149.1, 196.2. (Found: C, 54.0; H, 4.3; N, 3.8; $C_{17}H_{16}NOI$ requires C, 54.1; H, 4.2; N, 3.7%).

Fraction 2. 4-Chloro-2-pyrrolidinobenzophenone **10b** (0.26 g, 4%), δ_H 2.05 (4H, m, $(CH_2)_2$), 3.36 (4H, m, $N(CH_2)_2$), 6.42 (1H, dd, J=8.7 Hz, 2.3, 5-H), 6.57 (1H, d, J=2.4 Hz, 3-H), 7.36 (1H, d, J=8.6 Hz, 6-H), 7.43 (2H, m, 3′,5′-H), 7.54 (1H, m, 4′-H), 7.78 (2H, m, 2′,6′-H).

Fraction 3. 2,4-Dipyrrolidinobenzophenone **9** (0.29 g, 4%).

3.7.2. 2-Bromo-4-pyrrolidinobenzophenone 11b. From 2-bromo-4-chlorobenzophenone **8b**, elution from silica gave two fractions. *Fraction 1*. 2-Bromo-4-pyrrolidinobenzophenone **11b** as yellow microcrystals (2.95 g, 39%), mp 117–120 °C, ν_{max} 1642, 1593 cm^{-1}, δ_H 1.90 (4H, m, $(CH_2)_2$), 3.12 (4H, m, $N(CH_2)_2$), 6.64 (1H, dd, J=8.3, 1.9 Hz, 5-H), 6.81 (1H, d, J=1.9 Hz, 3-H), 7.17 (1H, d, J=8.3 Hz, 6-H), 7.46 (2H, m, 5′,3′-H), 7.56 (1H, m, 4′-H), 7.91 (2H, m, 2′,6′-H), δ_C 25.8, 51.3, 113.6, 114.7, 122.3, 127.3, 128.3, 130.4, 132.6, 132.8, 137.5, 138.1, 148.7, 195.8. (Found: C, 61.7; H, 5.3; N, 4.6; $C_{17}H_{16}NOBr$ requires C, 61.8; H, 4.9; N, 4.2%).

Fraction 2. 4-Chloro-2-pyrrolidinobenzophenone **10b** (0.33 g, 5%).

3.7.3. 2-Chloro-4-pyrrolidinobenzophenone 11c. From 2-chloro-4-fluorobenzophenone **8c**, elution from silica gave three fractions. *Fraction 1*. 2-Chloro-4-pyrrolidinobenzophenone **11c** as yellow microcrystals (3.35 g, 51%), mp 95–98 °C, ν_{max} 1650, 1591 cm^{-1}, δ_H 2.04 (4H, m, $(CH_2)_2$), 3.33 (4H, m, $N(CH_2)_2$), 6.41 (1H, dd, J=8.6, 2.4 Hz, 5-H), 6.56 (1H, d, J=2.4 Hz, 3-H), 7.35 (1H, d, J=8.6 Hz, 6-H), 7.43 (2H, m, 5′,3′-H), 7.52 (1H, m, 4′-H), 7.77 (2H, m, 2′,6′-H), δ_C 25.8, 48.0, 109.4, 113.2, 124.2, 128.6, 130.4, 132.7, 133.5, 135.0, 139.2, 150.4, 195.2. (Found: C, 71.3; H, 5.7; N, 4.9; $C_{17}H_{16}NOCl$ requires C, 71.5; H, 5.6; N, 4.9%).

Fraction 2. 4-Fluoro-2-pyrrolidinobenzophenone **10a** (60 mg, 1%).

Fraction 3. 2,4-Dipyrrolidinobenzophenone **9** (0.37 g, 5%).

3.7.4. 2-Fluoro-4-pyrrolidinobenzophenone 11d. From 2,4-difluorobenzophenone **8d**, elution from silica gave two fractions. *Fraction 1*. 2-Fluoro-4-pyrrolidinobenzophenone **11d** as yellow microcrystals (2.3 g, 37%), mp 86–90 °C, ν_{max} 1645, 1609, 1579 cm^{-1}, δ_H 2.06 (4H, m, $(CH_2)_2$), 3.36 (4H, m, $N(CH_2)_2$), 6.18 (1H, dd, J=14.0, 2.3 Hz, 3-H), 6.35 (1H, dd, J=8.8, 2.3 Hz, 5-H), 7.44 (2H, m, 5′,3′-H), 7.53 (1H, m, 4′-H), 7.58 (1H, d, J=8.6 Hz, 6-H), 7.60 (2H, m, 2′,6′-H), δ_C 25.4, 47.7, 97.9 (d, J=26.9 Hz), 107.3 (d, J=1.3 Hz), 113.2 (d, J=12.5 Hz), 128.0, 129.2 (d, J=1.6 Hz), 131.8, 133.5 (d, J=4.5 Hz), 139.9, 152.1 (d, J=12.3 Hz), 161.9, 164.4, 192.7. (Found: C, 75.3; H, 6.2; N, 5.4; $C_{17}H_{16}NOF$ requires C, 75.8; H, 6.0; N, 5.2%).

Fraction 2. 4-Fluoro-2-pyrrolidinobenzophenone **10a** as yellow microcrystals (1.7 g, 28%).

3.8. Preparation of 2-substituted 4-pyrrolidinobenzophenones (Method 2)

The halogenobenzophenone **8** (23 mmol) was dissolved in a mixture of pyrrolidine (5.85 mL, 70 mmol) and anhyd DMSO (30 mL) and stirred at room temperature for 10 min and then heated under reflux until TLC examination of the reaction mixture indicated that no further changes were apparent (~4 days). The cooled mixture was poured into water (300 mL) and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3×100 mL) and the combined organic phases were washed with water (6×50 mL), dried (anhyd Na_2SO_4) and evaporated to afford the crude product. Purification was effected by elution from silica with 30% EtOAc in hexane. The following benzophenones were prepared in this manner:

3.8.1. 2-Methoxy-4-pyrrolidinobenzophenone 11f. From 4-chloro-2-methoxybenzophenone **8f**, elution from silica gave two fractions. *Fraction 1*. 2-Methoxy-4-pyrrolidinobenzophenone **11f** as yellow microcrystals (1.16 g, 18%), mp 83–85 °C, ν_{max} 1630, 1592 cm^{-1}, δ_H 2.02 (4H, m, $(CH_2)_2$), 3.35 (4H, m, $N(CH_2)_2$), 3.69 (3H, s, OCH_3), 6.01 (1H, d, J=2.0 Hz, 3-H), 6.14 (1H, dd, J=8.6, 2.1 Hz, 5-H), 7.39 (2H, m, 6-H, Ar-H), 7.46 (2H, m, Ar-H), 7.70 (2H, m, 2′,6′-H), δ_C 25.9, 48.1, 55.7, 94.7, 104.0, 115.9, 128.1, 129.8, 131.6, 134.4, 141.0, 152.2, 161.3, 195.5. (Found: C, 76.7; H, 6.9; N, 4.9; $C_{18}H_{19}NO_2$ requires C, 76.8; H, 6.8; N, 5.0%).

Fraction 2. 2-Hydroxy-4-pyrrolidinobenzophenone **11e** as green microcrystals (1.17 g, 19%), mp 55–58 °C, ν_{max} 3435, 1628, 1549, 1522 cm^{-1}, δ_H 2.02 (4H, m, $(CH_2)_2$), 3.38 (4H, m, $N(CH_2)_2$), 6.05 (2H, m, 3,5-H), 7.38 (1H, d, J=8.6 Hz, 6-H), 7.48 (3H, m, Ar-H), 7.61 (2H, m, 2′,6′-H), 13.04 (1H, s, OH), δ_C 25.3, 47.6, 97.8, 104.3, 109.2, 128.1, 128.7, 130.7, 135.4, 139.0, 153.4, 166.0, 198.1. (Found: C, 76.0; H, 6.1; N, 4.9; $C_{17}H_{17}NO_2$ requires C, 76.4; H, 6.4; N, 5.2%).

3.8.2. 2-Methyl-4-pyrrolidinobenzophenone 11g. From 4-chloro-2-methylbenzophenone **8g**. As yellow microcrystals (2.5 g, 41%), mp 65–67 °C, ν_{max} 1631, 1608, 1577 cm^{-1}, δ_H 2.02 (4H, m, $(CH_2)_2$), 2.53 (3H, s, CH_3), 3.35 (4H, m, $N(CH_2)_2$), 6.31 (1H, dd, J=8.6, 2.3 Hz, 5-H), 6.42 (1H, d, J=2.2 Hz, 3-H), 7.33 (1H, d, J=8.6 Hz, 6-H),

7.42 (2H, m, 5′,3′-H), 7.49 (1H, m, 4′-H), 7.71 (2H, m, 2′,6′-H), δ_C 22.4, 25.9, 47.9, 107.8, 114.6, 124.7, 128.4, 130.2, 131.5, 131.8, 134.8, 140.9, 142.5, 150.1, 197.5. (Found: C, 81.4; H, 7.3; N, 5.2; $C_{18}H_{19}NO$ requires C, 81.5; H, 7.2; N, 5.3%).

3.9. Preparation of prop-2-yn-1-ols

n-Butyllithium (1.6 M in hexanes) (9.4 mL, 15 mmol) was added slowly via syringe to a cold (−10 °C), stirred solution of trimethylsilylacetylene (2.12 mL, 15 mmol) in anhyd tetrahydrofuran (60 mL) under nitrogen atmosphere. On completion of the addition (ca. 5 min) the cold solution was allowed to stir for 1 h. The pyrrolidinobenzophenone **11** (12 mmol) was added in a single portion and the mixture stirred until TLC examination of the reaction mixture indicated that none of the benzophenone remained (ca. 3 h). The reaction mixture was re-cooled to 0 °C and a solution of methanolic potassium hydroxide from potassium hydroxide (1.74 g, 31 mmol) in methanol (20 mL) was added in a single portion. The cooling bath was then removed and the mixture warmed to room temperature, after ca. 15 min TLC examination indicated that deprotection was complete. The mixture was acidified to pH ~7 using glacial acetic acid and then poured into water (500 mL). The organic layer was separated and the aqueous layer extracted with ethyl acetate (3×100 mL). The organic phases were combined, washed with water (3×50 mL) and dried (anhyd Na_2SO_4). Removal of the solvent gave the prop-2-yn-1-ol, which was recrystallised from hexane and ethyl acetate. The following alkynols were obtained in this way:

3.9.1. 1-(2-Chloro-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol 12a. From 2-chloro-4-pyrrolidinobenzophenone **11c** as a brown powder (3.2 g, 86%), mp 70–73 °C, ν_{max} 3285, 1607 cm^{-1}, δ_H 1.84 (4H, m, $(CH_2)_2$), 2.72 (1H, s, alkynic-H), 3.11 (4H, m, $N(CH_2)_2$), 3.42 (1H, br s, OH), 6.30 (1H, dd, J=8.8, 2.5 Hz, 5-H), 6.38 (1H, d, J=2.5 Hz, 3-H), 7.17 (3H, m, Ar-H), 7.40 (2H, m, 2′,6′-H), 7.54 (1H, d, J=8.7 Hz, 6-H). (Found: C, 73.0; H, 5.7; N, 4.5; $C_{19}H_{18}NOCl$ requires C, 73.2; H, 5.8; N, 4.5%).

3.9.2. 1-(2-Fluoro-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol 12b. From 2-fluoro-4-pyrrolidinobenzophenone **11d** as a pale brown powder (2.4 g, 67%), mp 76–80 °C, ν_{max} 3278, 1624 cm^{-1}, δ_H 1.99 (4H, m, $(CH_2)_2$), 2.84 (1H, s, alkynic-H), 2.90 (1H, br s, OH), 3.24 (4H, m, $N(CH_2)_2$), 6.19 (1H, dd, J=14.7, 2.4 Hz, 3-H), 6.27 (1H, dd, J=8.7, 2.4 Hz, 5-H), 7.31 (4H, m, Ar-H), 7.59 (2H, m, 2′,6′-H). (Found: C, 76.9; H, 6.0; N, 4.7; $C_{19}H_{18}NOF$ requires C, 77.2; H, 6.1; N, 4.7%).

3.9.3. 1-(2-Methoxy-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol 12c. From 2-methoxy-4-pyrrolidinobenzophenone **11f** as a pale brown powder (3.6 g, 98%), mp 75–78 °C, ν_{max} 3286, 1613 cm^{-1}, δ_H 1.99 (4H, m, $(CH_2)_2$), 2.78 (1H, s, alkynic-H), 3.28 (4H, m, $N(CH_2)_2$), 3.76 (3H, s, OCH_3), 4.91 (1H, br s, OH), 6.08 (1H, m, 3,5-H), 7.09 (1H, d, J=8.4 Hz, 6-H), 7.29 (3H, m, Ar-H), 7.56 (2H, m, 2′,6′-H). (Found: C, 78.2; H, 6.5; N, 4.3; $C_{20}H_{21}NO_2$ requires C, 78.2; H, 6.9; N, 4.6%).

3.9.4. 1-(2-Methyl-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol 12d. From 3-methyl-4-pyrrolidinobenzophenone **11g** as a pale brown gum (3.3 g, 96%), ν_{max} 3247, 1604 cm^{-1}, δ_H 1.82 (4H, m, $(CH_2)_2$), 1.91 (3H, s, CH_3), 2.64 (1H, br s, OH), 2.70 (1H, s, alkynic-H), 3.13 (4H, m, $N(CH_2)_2$), 6.19 (1H, d, J=2.4 Hz, 3-H), 6.27 (1H, dd, J=8.6, 2.4 Hz, 5-H), 7.13 (3H, m, Ar-H), 7.37 (2H, m, 2′,6′-H), 7.59 (1H, d, J=8.6 Hz, 6-H). Satisfactory elemental analysis could not be obtained for this compound.

3.10. Preparation of 3,3-diaryl-3*H*-naphtho[2,1-*b*]pyrans

A stirred solution of 2-naphthol (0.48 g, 3.3 mmol) and the prop-2-yn-1-ol **12** (3.3 mmol) in toluene (40 mL) was warmed to 50 °C. Acidic alumina (2.5 g) was added and the mixture was refluxed until TLC examination indicated that none of the prop-2-yn-1-ol remained (ca. 1.5 h). The mixture was cooled to ~50 °C, filtered and the alumina was washed with hot toluene (2×20 mL). Removal of the toluene from the combined washings and filtrate gave a gum that was eluted from silica (40% ethyl acetate in hexane) to afford the naphthopyran. The following naphthopyrans were obtained using this protocol:

3.10.1. 3-(2-Chloro-4-pyrrolidinophenyl)-3-phenyl-3*H*-naphtho[2,1-*b*]pyran 13a. From 1-(2-chloro-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol as pale pink microcrystals (0.79 g, 55%), mp 170–173 °C, ν_{max} 1607 cm^{-1}, δ_H 1.91 (4H, m, $(CH_2)_2$), 3.17 (4H, m, $N(CH_2)_2$), 6.31 (1H, dd, J=8.8, 2.6 Hz, Ar-H), 6.37 (1H, d, J=10.0 Hz, 2-H), 6.51 (1H, d, J=2.5 Hz, Ar-H), 7.19 (1H, d, J=8.8 Hz, 5-H), 7.27 (5H, m, Ar-H, 1-H), 7.44 (3H, m, Ar-H), 7.51 (1H, d, J=8.8 Hz, Ar-H), 7.62 (1H, d, J=8.8 Hz, 6-H), 7.68 (1H, d, J=8.4 Hz, 7-H), 7.94 (1H, d, J=8.5 Hz, 10-H). (Found: $[M+H]^+$437.1536; C, 79.1; H, 5.6; N, 3.2; $C_{29}H_{24}NOCl$ requires $[M+H]^+$437.1540; C, 79.5; H, 5.5; N, 3.2%).

3.10.2. 3-(2-Fluoro-4-pyrrolidinophenyl)-3-phenyl-3*H*-naphtho[2,1-*b*]pyran 13b. From 1-(2-fluoro-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol as light brown microcrystals (0.92 g, 66%), mp 179–182 °C, ν_{max} 1624 cm^{-1}, δ_H 1.96 (4H, m, $(CH_2)_2$), 3.21 (4H, m, $N(CH_2)_2$), 6.21 (2H, dd, J=25.1, 2.4 Hz, Ar-H and m, Ar-H), 6.30 (1H, dd, J=10.0, 3.6 Hz, 2-H), 7.19 (1H, d, J=8.8 Hz, 5-H), 7.26 (2H, m, Ar-H), 7.32 (3H, m, Ar-H, 1-H), 7.39 (1H, m, Ar-H), 7.44 (1H, m, Ar-H), 7.50 (2H, m, Ar-H), 7.64 (1H, d, J=8.8 Hz, 6-H), 7.71 (1H, d, J=8.5 Hz, 7-H), 7.96 (1H, d, J=8.8 Hz, 10-H). (Found: $[M+H]^+$422.1921; C, 82.5; H, 5.8; N, 3.3; $C_{29}H_{24}NOF$ requires $[M+H]^+$422.1920; C, 82.6; H, 5.7; N, 3.3%).

3.10.3. 3-(2-Methoxy-4-pyrrolidinophenyl)-3-phenyl-3*H*-naphtho[2,1-*b*]pyran 13c. From 1-(2-methoxy-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol as pale pink microcrystals (0.97 g, 68%), mp 153–155 °C, ν_{max} 1614 cm^{-1}, δ_H 1.95 (4H, m, $(CH_2)_2$), 3.25 (4H, m, $N(CH_2)_2$), 3.56 (3H, s, OCH_3), 6.07 (1H, d, J=2.1 Hz, Ar-H), 6.11 (1H, dd, J=8.5, 2.3 Hz, Ar-H), 6.45 (1H, d, J=10.2 Hz, 2-H), 7.21 (3H, m, Ar-H, 5-H), 7.25 (3H, m, Ar-H, 1-H), 7.42 (1H, m, Ar-H), 7.47 (3H, m, Ar-H), 7.61 (1H, d, J=8.8 Hz, 6-H), 7.68 (1H, d, J=8.6 Hz, 7-H), 7.93 (1H, d, J=8.5 Hz, 10-H). (Found: $[M+H]^+$434.2110; C, 82.9;

H, 6.4; N, 3.1; $C_{30}H_{27}NO_2$ requires $[M+H]^+$434.2110; C, 83.1; H, 6.3; N, 3.2%).

3.10.4. 3-(2-Methyl-4-pyrrolidinophenyl)-3-phenyl-3*H*-naphtho[2,1-*b*]pyran 13d. From 1-(2-methyl-4-pyrrolidinophenyl)-1-phenylprop-2-yn-1-ol as pale pink microcrystals (0.62 g, 45%), mp 170–172 °C, ν_{max} 1608 cm^{-1}, δ_H 1.92 (4H, m, $(CH_2)_2$), 2.23 (3H, s, CH_3), 3.22 (4H, m, $N(CH_2)_2$), 6.08 (1H, d, $J=9.9$ Hz, 2-H), 6.25 (1H, dd, $J=8.6$, 2.6 Hz, Ar-H), 6.35 (1H, d, $J=2.4$ Hz, Ar-H), 7.15 (1H, d, $J=8.8$ Hz, 5-H), 7.24 (2H, m, Ar-H), 7.30 (4H, m, Ar-H, 1-H), 7.46 (3H, m, Ar-H), 7.61 (1H, d, $J=8.8$ Hz, 6-H), 7.68 (1H, d, $J=8.8$ Hz, 7-H), 7.94 (1H, d, $J=8.4$ Hz, 10-H). (Found: $[M+H]^+$418.2169; C, 86.1; H, 6.5; N, 3.3; $C_{30}H_{27}NO$ requires $[M+H]^+$418.2165; C, 86.3; H, 6.5; N, 3.4%).

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References and notes

1. Mann, C.; Melzig, M.; Weigand, U. PCT WO 03/080595 A1, 2003. Chan, Y. -P.; Breyne, O.; Jean, P. PCT WO 01/36424 A2, 2001. Lin, J.; Van Gemert, B. PCT WO 99/31082, 1999. Clarke, D. A.; Heron, B. M.; Gabbutt, C. D.; Hepworth, J. D.; Partington, S. M.; Corns, S. N. PCT WO 98/42693 A1, 1998. Rickwood, M.; Smith, K. E.; Gabbutt, C. D.; Hepworth, J. D. PCT WO 94/22850, 1994. Garrity, N. E. U.S. Patent No. 6,174,464 B1, 2002. Momoda, J.; Matsuoka, S.; Nagou, H. U.S. Patent No. 6,525,194 B2, 2003.
2. McCallien, D. W. J.; Bezer, M. GB Patent No. 2344599, 2000.
3. Camus, M. Eur. Patent No. 488902, 1992. McDonald, L. J.; Ames, C. J.; Thomas, D. W.; Colgan, D. C. PCT WO 02/02319 A1, 2002.
4. Forest, S. E.; Krummen, M. S.; Yelton, J. A. PCT WO 02/03949 A2, 2002.
5. McManus, M., Federer, B. U.S. Patent No. 0,122,780 A1, 2002.
6. Compounds undergoing a thermally driven ring closure reaction are said to exhibit T-type photochromism; Bouas-Laurent, H.; Dürr, H. *Pure Appl. Chem.* **2001**, *73*, 639.
7. Frigoli, M.; Moustrou, C.; Samat, A.; Guglielmetti, R. *Eur. J. Org. Chem.* **2003**, 2799. Salvador, M. A.; Coelho, P. J.; Burrows, H. D.; Oliveira, M. M.; Carvalho, L. M. *Helv. Chim. Acta* **2004**, *87*, 1400. Gentili, P. L.; Romani, A.; Becker, R. S.; Favaro, G. *Chem. Phys.* **2005**, *309*, 167. Delbaere, S.; Micheau, J. -C.; Vermeersch, G. *J. Org. Chem.* **2003**, *68*, 8968. Gabbutt, C. D.; Heron, B. M.; Thomas, D. A.; Light, M. E.; Hursthouse, M. B. *Tetrahedron Lett.* **2004**, *45*, 6151. Ahmed, S. A.; Sallenave, X.; Fages, F.; Mieden-Gundert, G.; Müller, W. M.; Müller, U.; Vögtle, F.; Pozzo, J.-L. *Langmuir* **2002**, *18*, 7096.
8. Van Gemert, B. In *Organic Photochromic and Thermochromic Compounds*; Crano, J. C., Guglielmetti, R. J., Eds.; Main Photochromic Families; Plenum: New York, 1998; Vol. 1, p 113. Hepworth, J. D.; Gabbutt, C. D.; Heron, B. M. In *Colour Science '98*; Griffiths, J., Ed.; Dye and Pigment Chemistry; University of Leeds: Leeds, 1999; Vol. 1, p 161.
9. Van Gemert, B.; Bergomi, M. P. U.S. Patent No. 5,066,818, 1991.
10. Gabbutt, C. D.; Heron, B. M.; Instone, A. C. *Heterocycles* **2003**, *60*, 843.
11. Gabbutt, C. D.; Heron, B. M.; Instone, A. C.; Horton, P. N.; Hursthouse, M. B. *Tetrahedron* **2005**, *61*, 463.
12. Preliminary communication of our results as an invited lecture at the 10th International Conference on Dyes, Pigments and Functional Dyes, Colorchem '04, Czech Republic, May 2004.
13. Hodgson, H. H. *Chem. Rev.* **1947**, *40*, 251. Zollinger, H. *Angew. Chem.* **1978**, *90*, 151. Nonhebel, D. C. *J. Chem. Soc. (Special Publication)* **1970**, 409.
14. Rizzi, G. P. *Synth. Commun.* **1983**, *13*, 1173.
15. Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
16. Gabbutt, C. D.; Heron, B. M.; McCreary, J. C.; Thomas, D. A. *J. Chem. Res. S* **2002**, 69.
17. Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M.; Partington, S. M.; Thomas, D. A. *Dyes and Pigments* **2001**, *49*, 65. Gabbutt, C. D.; Gelbrich, T.; Hepworth, J. D.; Heron, B. M.; Hursthouse, M. B.; Partington, S. M. *Dyes and Pigments* **2002**, *54*, 79.
18. Iwai, I.; Ide, J. *Chem. Pharm. Bull.* **1962**, *10*, 926.
19. Barberis, C.; Campredon, M.; Lokshin, V.; Giusti, G.; Faure, R. *Magn. Reson. Chem.* **1995**, *33*, 977. Delbaere, S.; Teral, Y.; Bochu, C.; Campredon, M.; Vermeersch, G. *Magn. Reson. Chem.* **1999**, *37*, 159.
20. Clarke, D. A.; Heron, B. M.; Gabbutt, C. D.; Hepworth, J. D.; Partington, S. M.; Corns, S. N. PCT WO 98/45281 A1, 1998.
21. Gabbutt, C. D.; Hepworth, J. D.; Heron, B. M. Unpublished results. See also: Harié, G.; Samat, A.; Guglielmetti, R.; De Keukeleire, D.; Saeyens, W.; Van Parys, I. *Tetrahedron Lett.* **1997**, *38*, 3075 for an example of symmetrically substituted 3*H*-naphtho[2,1-*b*]pyrans with multiple absorption bands.
22. Collings, P. J.; Hird, M. *Introduction to Liquid Crystals: Chemistry and Physics*; Taylor Francis: London, 1997; p 70. Hatano, Y. In *Chemistry and Applications of Leuco Dyes*; Muthyala, R., Ed.; Plenum: New York, 1997; p 176.
23. Clarke, D. A.; Heron, B. M.; Gabbutt, C. D.; Hepworth, J. D.; Partington, S. M.; Corns, S. N. PCT WO 00/18755 A1, 2000.
24. Rickwood, M., Hepworth, J. D., Gabbutt, C. D., PCT WO 95/05382 A1, 1995. Guglielmetti. R., Pozzo, J. L., Samat, A. U.S. Patent No. 5,527,911 A, 1996.
25. Pelz, K.; Ernest, I.; Alderova, E.; Metysova, J.; Protiva, M. *Collect. Czech. Chem. Commun.* **1968**, *33*, 1852.
26. Cam-Van, N. T.; Diep, B. K.; Buu-Hoi, N. P. *Tetrahedron* **1964**, *20*, 2195.
27. Zhang, C.; Wang, Z. Y. *Macromolecules* **1993**, *26*, 2234.
28. Perrot, C.; Cerutti, E. *Bull. Soc. Chim. Fr.* **1974**, 2225.
29. Aeberli, P.; Eden, P.; Gogerty, J. G.; Houlihan, W. J.; Penberthy, C. *J. Med. Chem.* **1975**, *18*, 177.