Use of Functionalised Ynamines in a Hetero-Diels–Alder Approach to Dihydronaphtho[1,2-*b*]pyrans and Indeno[1,2-*b*]pyrans[1]

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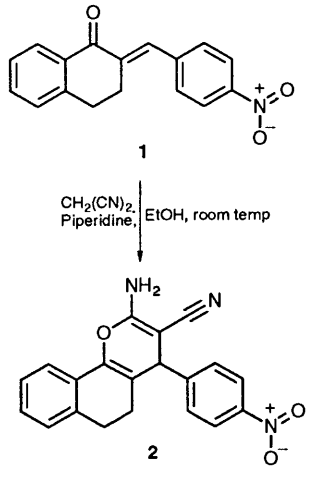
Reaction of the ynamine ester methyl 3-(pyrrolidin-1-yl)prop-2-ynoate **5** with 2-(4-nitrobenzylidene)-1-tetralone **1** results in a very poor yield of the chromatographically labile 4-aryl-5,6-dihydro-4*H*-naphtho[1,2-*b*]pyran **8** along with the α-pyrone **10**. Increasing the reactivity of the 4π component by using the 2-arylidene indan-1,3-diones **11**–**13** results in moderate to good yields of the 4-aryl-5-oxo-4*H*-indeno[1,2-*b*]pyran-3-carboxylates **14**–**19**. An ynamine nitrile **24**, generated *in situ*, also reacts with **12** and **13**, furnishing rather lower yields of the adducts **20** and **21**.

Our interest in the biological activity[2] of a series of 2-amino-5,6-dihydro-4*H*-naphtho[1,2-*b*]pyran-3-carbonitriles[3] such as **2** recently made it necessary to investigate synthetic routes to related species in which the enamine NH_2 was replaced by an *N*,*N*-dialkyl substituent and in which the nitrile functionality could be replaced by other electron-withdrawing groups. Flexible synthetic routes allowing this variety were sought, as the approach to **2** is limited[3,4] (Scheme 1).

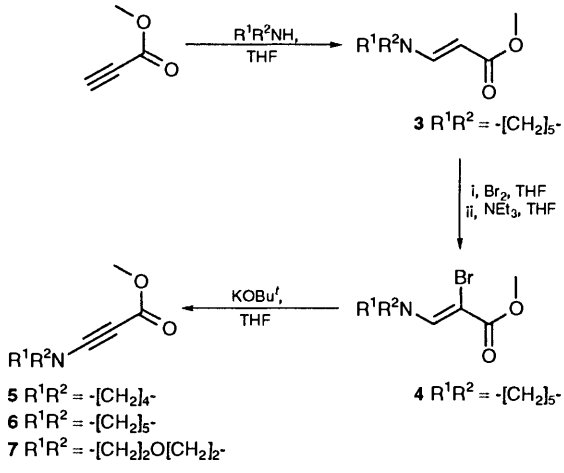


Scheme 1

Replacement of malononitrile in the reaction with arylidenetetralones by other active methylene species such as methyl cyanoacetate or cyanoacetamide reportedly leads[5] to α-pyrones, dihydropyridones or pyridones, depending on the reaction conditions employed, rather than the desired dihydronaphthopyrans. Additionally, the lability of the dihydronaphthopyran nucleus to both basic[3] and acidic[4] media makes functional group manipulation in this series a non-trivial exercise. With these considerations in mind, we opted to examine a hetero-Diels–Alder approach to assembling the pyran ring,[6–14] using the same arylidenetetralone **1** as the heterodiene component. Such a strategy would necessitate the use of functionalised ynamines such as **5**. Whilst the use of simple ynamines[15] in pyran synthesis has been described,[16–20] additionally functionalised ynamines have not received such attention. Indeed, the reduced reactivity of these 'push–pull' acetylenes means that they typically require a very reactive partner such as diphenylketene,[21,22] phenyl isocyanate[21] or ethyl diazoacetate[21] to undergo cyclisation reactions.

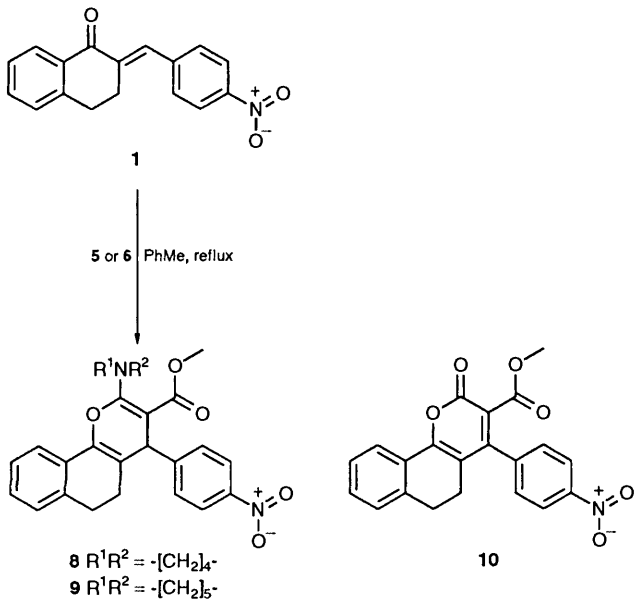
Results and Discussion

For our initial studies, the ynamine esters **5**–**7** were prepared. The method used involved a three-step sequence (Scheme 2)



Scheme 2

paralleling the known route[21] to methyl 3-(dimethylamino)-prop-2-ynoate. This could routinely be run on a reasonable scale without purification of the intermediates with the ynamine product being distilled at the end of the sequence. When a solution of the ynamine **5** (1.5 equiv.) and the arylidenetetralone **1** was heated in toluene at reflux for 120 h a substantial new component appeared (TLC). Residual compound **1** precipitated out on cooling of the mixture. Chromatography yielded a further quantity of **1** and then a mixture of two co-eluting materials (Scheme 3). Trituration of this mixture with acetone left behind a yellow solid (*vide infra*). The soluble material on repeated chromatography provided the pyran **8** in very low yield. This was disappointing since TLC had indicated reasonable progression of the reaction and probably reflects the instability of this type of compound to chromatography. The identity of **8** was fully confirmed by spectroscopic and microanalytical data: for example, a parent mass ion at *m*/*z* 433, a carbonyl band in the IR at 1693 cm^{-1} and signals in the ^1H NMR spectrum indicative of the 4-nitrophenyl group (8.15, 2 H, d and 7.52, 2 H, d), the pyran 4-H proton (4.42, 1 H, s) and the methyl ester (3.52, 3 H, s). Interestingly, the four protons of the pyrrolidine ring that are adjacent to nitrogen appeared as two well-separated multiplets (3.79, 2 H, m and 3.25, 2 H, m). The yellow solid that had separated out on trituration with acetone was also investigated spectroscopically. The ^1H NMR spectrum indicated the presence of the 4-nitrophenyl and dihydro-



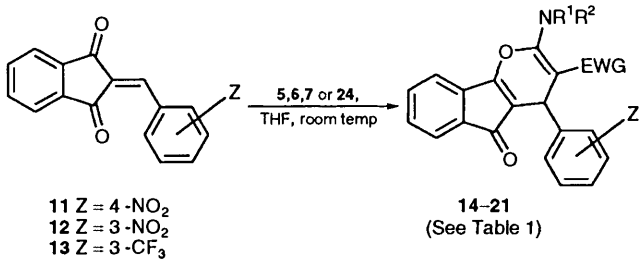
Scheme 3

Table 1

R^1R^2	EWG	Z	Compound (Yield/%)
$-[CH_2]_4-$	CO_2Me	4-NO_2	**14** (32)
$-[CH_2]_4-$	CO_2Me	3-NO_2	**15** (43)
$-[CH_2]_5-$	CO_2Me	3-NO_2	**16** (50)
$-[CH_2]_5-$	CO_2Me	4-NO_2	**17** (37)
$-[CH_2]_5-$	CO_2Me	3-CF_3	**18** (28)
$-[CH_2]_2O[CH_2]_2-$	CO_2Me	4-NO_2	**19** (39)
$-[CH_2]_2O[CH_2]_2-$	CN	4-NO_2	**20** (11)
$-[CH_2]_2O[CH_2]_2-$	CN	3-CF_3	**21** (10)

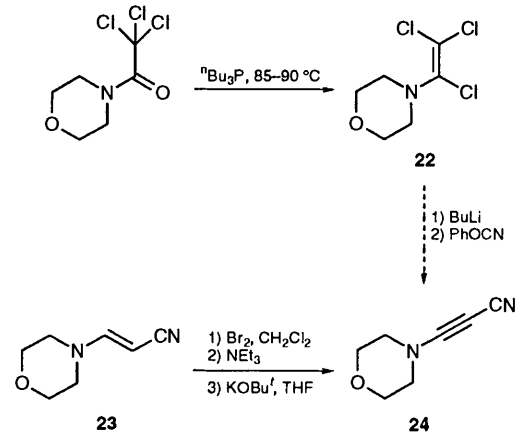
naphthalene protons but the absence of the 4*H*-pyran proton seen for compound **8**. The ^{13}C NMR spectrum showed two carbonyl carbons at 163.4 and 156.8 ppm, supported by the presence in the IR spectrum of two carbonyl bands at 1740 and 1703 cm^{-1}. There was long-wavelength absorption in the UV spectrum at 382 nm. A parent ion at *m/z* 378 was noted in the mass spectrum. All this evidence pointed towards the α-pyrone structure **10** and this was confirmed by microanalysis. It is likely that the α-pyrone **10** arose from the pyran **8** by hydrolysis during the repeated chromatography necessary during the purification process. Repeating this reaction using the ynamine ester **6** resulted in the isolation of the pyran **9** in an improved yield (14%). The α-pyrone **10** was not isolated in this instance, presumably due to the shortened purification procedure used.

In probing the scope of this reaction, it was found that the use of xylene rather than toluene failed to give the desired product (either due to rapid polymerisation of the ynamine or decomposition of the pyran), the use of a Lewis acid (*e.g.* magnesium bromide–diethyl ether) failed to noticeably accelerate the reaction (indeed it seemed to catalyse decomposition of the product) and the use of substituent patterns other than 4-nitrophenyl (4-chlorophenyl and 4-methoxyphenyl) in the arylidenetetralone **1** failed to yield the pyran. It thus became clear that in order to prepare some type of multiply functionalised pyran close to the original target by this route, the reactivity of the heterodiene component needed to be enhanced. The first logical choice was to move to the 2-arylideneindan-1,3-dione nucleus, exemplified here by compounds **11–13**, which possess activation by two carbonyl groups. Such compounds are highly reactive both as Michael acceptors[23–26] and in the hetero-Diels–Alder reaction where they are known to form pyrans by reaction with enol ethers,[27] ketene acetals[27] and phosphacumulenes.[28] This proved to serve as good precedent, since reaction of the ynamine ester **5** with the arylideneindandione **11** proceeded smoothly in THF at room temperature providing the indenopyran **14** in 32% isolated yield. The structure of **14** was assigned on the basis of spectroscopic and microanalytical data. In this case, the regiochemistry of the addition was confirmed by a nuclear Overhauser effect difference experiment: irradiation of the ester CO_2Me resulted in enhancement of the pyran 4-H and both the 2 and 6 protons of the pendant 4-nitrophenyl group. This successful reaction was then used to generate a number of other indeno[1,2-*b*]pyran-3-carboxylates **15–19** (Scheme 4) in modest yields (Table 1) for our structure–activity relationship studies.



Scheme 4

Although the ynamine esters **5–7** were prepared in a straightforward fashion, problems were encountered with the preparation of ynamine nitriles. Even though a number are described in the literature,[29,30] preparation of a potential key intermediate 3-chloropropynenitrile[31] was not possible on the tens-of-grams scale that we required. Similarly, we were unable to clean up the trichloroenamine[32] **22** adequately to allow conversion *via* the proposed sequential treatment with butyllithium[29,33] and phenyl cyanate[34] into the target compound **24** (Scheme 5).



Scheme 5

We returned to the bromination–dehydrobromination sequence using the nitrile **23** as the starting material.[35] Bromination of this material proceeded well as evidenced by ^1H NMR analysis, but treatment with potassium *tert*-butoxide in THF followed by distillation failed in all cases to yield any ynamine nitrile **24**. We then attempted to generate **24** from its brominated precursor at low temperature in the presence of an arylideneindenedione as a trapping species. This succeeded and we were able to isolate the desired indeno[1,2-*b*]pyran-3-carbonitriles **20** and **21**, albeit in low yields (Table 1). Such yields are not uncommon in reactions involving ynamine nitriles[29,36]

Table 2 Microanalytical and spectroscopic data

Compound	M.p. (°C)	Found (%) (Required) C	H	N	ν_{max}/cm^{-1}	λ_{max}/nm
14	189–191	66.5 (66.7)	4.9 (4.7)	6.3 (6.5)	1692	238, 244, 264
15	187–190	66.4 (66.7)	4.7 (4.7)	6.3 (6.5)	1700, 1695	246, 295
16	187–188.5	67.0 (67.3)	5.2 (5.0)	6.2 (6.3)	1700, 1696	240, 245
17	190–191	67.3 (67.3)	5.1 (5.0)	6.3 (6.3)	1706, 1701	239, 244, 269
18	163–164	66.3 (66.5)	4.7 (4.7)	3.2 (3.0)	1699, 1663	240, 245
19	191–194	64.5 (64.3)	4.7 (4.5)	6.1 (6.25)	1700, 1696	238, 244, 264
20	260–264	66.6 (66.5)	4.3 (4.1)	9.8 (10.1)	2201, 1705	242, 257
21	212–215	65.5 (65.7)	4.1 (3.9)	6.6 (6.4)	2192, 1708	244

Table 3 Spectroscopic data

Compound	*m/z*	δ_H/ppm
14	433 (100), 403 (9), 373 (7), 310 (7), 172 (22)	8.11 (2 H, d, *J* 8), 7.50 (2 H, d, *J* 8), 7.41 (1 H, d, *J* 7), 7.35 (1 H, t, *J* 7), 7.30 (1 H, t, *J* 7), 7.15 (1 H, d, *J* 7), 4.90 (1 H, s), 3.90 (2 H, m), 3.60 (3 H, s), 3.32 (2 H, m), 3.10 (2 H, m) and 2.96 (2 H, m)
15	433 (100), 403 (20), 375 (6), 345 (3)	8.11 (1 H, t, *J* 2), 8.02 (1 H, bd, *J* 8), 7.77 (1 H, bd, *J* 8), 7.26–7.46 (4 H, m), 7.17 (1 H, bd, *J* 7), 4.92 (1 H, s), 3.93 (2 H, m), 3.61 (3 H, s), 3.34 (2 H, m) and 1.95–2.11 (4 H, m)
16	447 (100), 415 (4), 387 (28), 324 (10)	8.05 (1 H, bd, *J* 8), 8.04 (1 H, bs), 7.73 (1 H, bd, *J* 8), 7.60 (1 H, t, *J* 8), 7.49 (1 H, m), 7.38–7.42 (3 H, m), 4.74 (1 H, s), 3.60 (2 H, m), 3.57 (3 H, s), 3.18 (2 H, m) and 1.58–1.80 (6 H, m)
17	447 (100), 415 (3), 387 (36), 324 (7)	8.16 (2 H, bd, *J* 9), 7.52 (2 H, bd, *J* 9), 7.51 (1 H, d, *J* 7), 7.38–7.42 (3 H, m), 4.71 (1 H, s), 3.56 (3 H, s), 3.55 (2 H, m), 3.17 (2 H, m) and 1.60–1.78 (6 H, m)
18	470 (100), 438 (6), 410 (49), 324 (23)	7.38–7.55 (8 H, m), 4.68 (1 H, s), 3.60 (2 H, m), 3.56 (3 H, s), 3.15 (2 H, m) and 1.56–1.78 (6 H, m)
19	449 (100), 419 (13), 389 (7), 326 (11), 250 (4)	8.15 (2 H, d, *J* 9), 7.54 (2 H, d, *J* 9), 7.33–7.55 (4 H, m), 4.74 (1 H, s), 3.80 (4 H, m), 3.56 (3 H, s) and 3.20–3.40 (4 H, m)
20	433 (66), 416 (100), 386 (15), 293 (32)	8.21 (2 H, d, *J* 9), 7.66 (2 H, d, *J* 9), 7.39–7.57 (4 H, m), 4.72 (1 H, s) and 3.51–3.73 (8 H, m)
21	456 (19), 439 (100), 293 (17)	7.73 (1 H, bs), 7.38–7.65 (7 H, m), 4.70 (1 H, s) and 3.50–3.72 (8 H, m)

Table 4 Inhibition of rat synovial fibroblast proliferation

Compound	% Inhibition at 50 μmol dm^{-3} [drug]	IC_{50}/μmol dm^{-3}
2	75.0	26.1
8	21.4	—
14	27.7	—
15	22.6	—
16	9.4	—
17	27.8	—
18	14.8	—
19	96.5	18.5

and, in this case, yield was of secondary importance. A number of the compounds were tested for their ability to inhibit the natural proliferation of rat synovial fibroblasts (Table 4).

For those compounds exhibiting a greater than 50% inhibition of proliferation at 50 micromolar concentration of drug, additional testing was carried out at lower concentrations and an IC_{50} generated. Compound **19** was the only one to exhibit activity (the dihydronaphthopyran **2** is used here as a comparator since in our hands it has been found to possess weak antiproliferative activity). The level of activity associated with these new compounds discouraged any further work on this part of the structure–activity relationship.

Experimental

M.p.s were determined on a Reichert hot-stage apparatus and are uncorrected. IR spectra were recorded on a Bruker IFS 48 instrument using KBr discs. UV spectra were determined on a Philips PU8725 instrument as methanol solutions. Mass spectra were recorded using a VG7070E instrument. NMR spectra were obtained for dilute solutions in deuteriated dimethyl sulfoxide ([$^2H_6$]DMSO), on a Bruker AM300 or AC300 instrument (300 MHz) unless otherwise indicated. Signals are reported downfield from TMS. *J* Values are recorded in Hz. Microanalyses were carried out by the Molecular Structure Research Group at Eli Lilly and Company, Indianapolis.

Preparation of 2-(4-*Nitrobenzylidene*)-3,4-*dihydronaphthalen*-1(2H)-*one* **1**.—A mixture of 3,4-dihydronaphthalen-1(2*H*)-one (21.9 g, 150 mmol), 4-nitrobenzaldehyde (150 mmol) and toluene-*p*-sulfonic acid (50 mg) was stirred and brought to reflux with removal of the water. After 7 h, heating was ceased and the mixture allowed to cool to room temperature. It was then stirred overnight, after which the voluminous yellow–orange solid was collected, washed with toluene and dried *in vacuo* to provide the title compound **1** as a yellow solid (31.5 g, 75%), m.p. 188–190 °C (lit.,[37] 192–193 °C).

'One-pot' Preparation of Methyl 3-(Piperidin-1-yl)prop-2-ynoate **6**.—To a stirred solution of methyl propiolate (16.93 g, 201 mmol) in dry THF (200 cm^3) at room temperature was added dropwise, during 30 min, a solution of piperidine (17.03 g, 200 mmol) in dry THF (50 cm^3). The solution turned yellow and there was a weak exotherm. The solution was stirred at room temperature for 18 h and then cooled to −15 °C under a nitrogen atmosphere [some of the enamine product **3** can precipitate out at this point: $\delta_H(CDCl_3)$ 7.40 (1 H d, *J* 13.5), 4.62 (1 H, d, *J* 13.5), 3.65 (3 H, s), 3.18 (4 H, m) and 2.60 (6 H, m)]. Bromine (32.9 g, 206 mmol) was added dropwise to the efficiently stirred mixture and the temperature was maintained at or just below −10 °C (1 h taken for the addition). The resulting heavy orange suspension was stirred at −10 °C for a further 30 min, when dry triethylamine (27.8 cm^3, 199 mmol) was added slowly, the temperature being maintained at −10 °C (25 min taken, no real exotherm during the addition). The mixture was stirred at −10 °C for a further 1 h and then filtered. The collected triethylamine hydrobromide was washed with cold (0 °C), dry THF–dichloromethane (1:1; 200 cm^3) and the filtrate concentrated under reduced pressure at a bath temperature of 5–10 °C. The thick, oily red–black residue **4** [$\delta_H(CDCl_3)$ 7.78 (1 H, s), 3.75 (3 H, s), 3.62 (4 H, m) and 2.63 (6 H, m)] was taken up in dry THF (200 cm^3) and stirred under nitrogen at room temperature during the addition of a solution of potassium *tert*-butoxide (20.2 g, 180 mmol) in dry THF (100 cm^3). The reaction was exothermic (temperature reached 40 °C). A precipitate (KBr) appeared instantly. The mixture was stirred for a further 45 min and then filtered through a pad of Kieselguhr, which was washed with dry THF. The red–black solution was concentrated under reduced pressure and the resulting viscous oil distilled using a Kugelrohr apparatus, to afford the *methyl propynoate* **6** as a yellow oil (15.8 g, 52% overall); b.p. 165 °C (oven)/1 mmHg; ν_{max}(film)/cm^{-1} 2188 and 1688; $\delta_H(CDCl_3)$ 3.65 (3 H, s), 3.18 (4 H, m) and 1.65 (6 H, m) [Found: *m/z* 335.1973. $C_{18}H_{27}N_2O_4$ $(2M + H)^+$ requires 335.1971].

Prepared in an analogous way were compounds **5** and **7**. Data for *methyl 3-(pyrrolidin-1-yl)prop-2-ynoate* **5**: ν_{max}(film)/cm^{-1} 2187 and 1685; $\delta_H(CDCl_3)$ 3.68 (3 H, s), 3.40 (4 H, m) and 1.90 (4 H, m) (Found: *m/z* 154.0957. $C_8H_{11}NO_2$ requires 154.0970). The ynamine ester **7** has been described recently.[38]

Preparation of the Pyran **8** *and the α-Pyrone* **10**.—To a stirred suspension of compound **1** (8.38 g, 30.0 mmol) in dry toluene (125 cm^3) was added the ester **5** (4.60 g, 30.0 mmol). The mixture was heated to reflux and stirred at this temperature for 120 h [after 67 h further ester **5** (2.30 g, 15.0 mmol) was added]. The solution was allowed to cool to room temperature whereupon the remaining ketone **1** precipitated out. This was filtered off, washed with toluene and dried *in vacuo* (2.95 g, 35% recovery). The filtrate was concentrated to yield a red oil. Flash chromatography on silica (ethyl acetate–hexane, 1:1) yielded a further quantity of **1** (1.14 g, 14% recovery) followed by an oil enriched in the pyran **8**. Trituration of this oil with acetone yielded *methyl 4-(4-nitrophenyl)-2-oxo-5,6-dihydro-2H-naphtho[1,2-b]pyran 3-carboxylate* **10** as a bright-yellow insoluble solid (142 mg, 1%); m.p. 232–237 °C (Found: C, 66.6; H, 4.2; N, 3.7. $C_{21}H_{15}NO_6$ requires C, 66.8; H, 4.0; N, 3.7%); ν_{max}/cm^{-1} 1740 and 1703; λ_{max}/nm 265 and 382; δ_H 8.37 (2 H, d, *J* 8), 7.78 (1 H, m), 7.65 (2 H, d, *J* 8), 7.45 (2 H, m), 7.34 (1 H, m), 3.50 (3 H, s), 2.85 (2 H, m) and 2.33 (2 H, m); *m/z* 378 (100%), 363 (9), 349 (9) and 280 (5). The acetone-soluble material was rechromatographed on neutral grade 3 alumina (ethyl acetate–hexane, 1:4), then silica (ethyl acetate–hexane, 1:1) and finally Florisil (ethyl acetate–hexane, 1:4). The resulting oil was triturated with hexane to yield *methyl 4-(4-nitrophenyl)-2-(pyrrolidin-1-yl)-5,6-dihydro-4H-naphtho[1,2-b]pyran-3-carboxylate* **8** as a crisp yellow foam [272 mg, 2% (4% based on recovered starting material)]; m.p. 155–159 °C (Found: C, 69.2; H, 5.8; N, 6.4. $C_{25}H_{24}N_2O_5$ requires C, 69.4; H, 5.6; N, 6.2%); ν_{max}/cm^{-1} 1693; λ_{max}/nm 272; δ_H 8.15 (2 H, d, *J* 8), 7.52 (2 H, d, *J* 8), 7.45 (1 H, m), 7.15–7.30 (3 H, m), 4.42 (1 H, s), 3.79 (2 H, m), 3.52, (3 H, s), 3.25 (2 H, m), 2.90 (1 H, m), 2.70 (1 H, m), 2.20 (1 H, m), 2.00 (3 H, m) and 1.80 (2 H, m); *m/z* 433 (100%), 403 (16), 373 (12) and 310 (12).

In an analogous fashion, the arylidene naphthalenone **1** (558 mg, 2.0 mmol) and the ynamine ester **6** (400 mg, 2.39 mmol) in dry toluene (10 cm^3) were heated under reflux for 96 h [further ester **6** (200 mg, 1.2 mmol) was added after 24 h]. On cooling of the mixture to room temperature, the remaining arylidene-naphthalenone **1** (214 mg, 38% recovery) was isolated. Chromatography of the concentrated filtrate on neutral grade 3 alumina (ethyl acetate–hexane, 15:85) yielded an orange gum (350 mg) which was a mixture of compounds. Rechromatography on Florisil (ethyl acetate–hexane, 15:85) provided a yellow solid (275 mg) which was passed through a short pad of neutral grade 3 alumina (ethyl acetate–hexane, 1:9) to furnish *methyl 4-(4-nitrophenyl)-2-(piperidin-1-yl)-5,6-dihydro-4H-naphtho[1,2-b]pyran-3-carboxylate* **9** as a glass [84 mg, 14% isolated yield (22.5% based on recovered starting material)]; ν_{max}/cm^{-1} 1692; λ_{max}/nm 272; δ_H 8.18 (2 H, d, *J* 8), 7.51 (2 H, d, *J* 8), 7.42 (1 H, m), 7.16–7.35 (3 H, m), 4.40 (1 H, s), 3.65 (2 H, m), 3.56 (3 H, s), 3.20 (2 H, m), 2.92 (1 H, m), 2.63 (1 H, m), 2.40 (1 H, m), 2.14 (1 H, m) and 1.60–1.81 (6 H, m); *m/z* 447 (100%), 417 (20), 387 (4) and 324 (8) [Found: $(M + H)^+$ 447.1937. $C_{26}H_{26}N_2O_5$ requires $(M + H)^+$ 447.1920].

Representative Procedure for the Arylidene Indandiones **11**–**13**.—To a stirred mixture of indan-1,3-dione (5.95 g, 40.7 mmol) and 4-nitrobenzaldehyde (6.15 g, 40.7 mmol) in ethanol (150 cm^3) at room temperature was added piperidine (3 drops). An immediate red–brown colour developed followed by the appearance of a heavy precipitate. After 1 h, the yellow solid was filtered off, washed with ethanol and stirred further with ethanol (200 cm^3) for 2.5 h. The solid was filtered off, washed with ethanol and dried *in vacuo* to provide *2-(4-nitrobenzylidene)indan-1,3-dione* **11** as a yellow solid (8.4 g, 74%), m.p. 229–230 °C (lit.,[39] 231 °C).

Similarly prepared were *2-(3-nitrobenzylidene)indan-1,3-dione* **12** (80% yield, m.p. 245–247 °C, lit.,[39] 250 °C) and *2-(3-trifluoromethylbenzylidene)indan-1,3-dione* **12** (67% yield, m.p. 153 °C (diethyl ether–hexane) (Found: C, 67.7; H, 3.1; F, 19.0. $C_{17}H_9F_3O_2$ requires C, 67.6; H, 3.00; F, 18.9%); ν_{max}/cm^{-1} 1733 and 1691; λ_{max}/nm 263 and 333; $\delta_H(CDCl_3)$ 8.84 (1 H, s), 8.60 (1 H, d, *J* 8), 8.08 (2 H, m), 7.92 (4 H, m) and 7.83 (1 H, t, *J* 8); *m/z* 320 (67%), 302 (100), 274 (9) and 233 (37).

Representative Procedure for the Indeno[1,2-b]pyran-3-carboxylates **14**–**19**.—To a stirred suspension of the indandione **11** (7.15 g, 25.6 mmol) in dry THF (125 cm^3) at room temperature was added dropwise over 5 min the propynoate **5** (6.85 g, 44.7 mmol). There was a slight exotherm and the bulk of the indandione **11** dissolved. After 2 h, additional indandione **11** (3.60 g, 12.9 mmol) was added to the mixture. After 15 h, the brown–black solution was concentrated to give a viscous gum which was triturated with dichloromethane. The supernatant solution was then concentrated and treated with hexane–diethyl ether (2:1) to induce solidification. The solid was stirred with methanol, filtered, washed with methanol and dried *in vacuo* to furnish *methyl 4-(4-nitrophenyl)-5-oxo-2-(pyrrolidin-1-yl)-4H-indeno[1,2-b]pyran-3-carboxylate* **14** as a yellow solid (5.33 g, 32%). For spectral and microanalytical characterisation, see Tables 2 and 3.

The esters **15**–**17** and **19** were prepared in a similar manner and purified using the same solvent combinations. The ester **18**

was obtained as a black oil which was triturated with hexane to produce a semi-solid. The hexane was decanted and the residue stirred with diethyl ether to provide **18** as a pale yellow powder.

Procedure for the Indeno[1,2-b]*pyrancarbonitrile* **20**.—To a stirred solution of the enamine nitrile **23**[35] (8.30 g, 60.0 mmol) in dichloromethane (200 cm^3) at −60 °C under nitrogen was added dropwise over 10 min bromine (10.1 g, 63.0 mmol). A heavy precipitate appeared and the solution turned red. The mixture was stirred at −60 °C for 10 min after which the cooling bath was removed and the temperature allowed to rise to −10 °C. The mixture was then recooled to −60 °C and a solution of triethylamine (6.35 g, 62.7 mmol) in diethyl ether (15 cm^3) added dropwise to it over 10 min (no exotherm). The cooling bath was removed and the temperature allowed to rise to 0 °C. After 35 min at this temperature, the heavy sandy brown suspension was filtered. The collected triethylamine hydrobromide was washed with dichloromethane (5.37 g after drying). The filtrate was concentrated under reduced pressure, the bath temperature being maintained at 5 °C, and the residue treated with THF. More triethylamine hydrobromide precipitated at this point which was collected, washed and dried as above (4.40 g). The filtrate was again concentrated under reduced pressure at 5 °C and the resulting viscous, red oil, free of triethylamine hydrobromide, used immediately in the next step.

The oil was dissolved in dry THF (150 cm^3) and half of this solution taken and cooled to −60 °C with stirring under nitrogen. To this was added a solution of potassium *tert*-butoxide (2.81 g, 25.0 mmol) in THF (20 cm^3) over 10 min at −60 °C (no exotherm). The solution darkened and TLC showed the disappearance of the spot corresponding to the bromo enamine. After 30 min at −60 °C, the cooling bath was removed. Once the temperature had reached −20 °C, the indandione **11** (2.79 g, 10.0 mmol) was added as a solid to the mixture which was then allowed to warm to room temperature; by this time it had turned brown and a precipitate had appeared. The mixture was stirred at room temperature overnight and then rapidly filtered under vacuum through a pad of flash silica (15 cm deep by 10 cm wide), eluting further with diethyl ether (1 dm^3). The filtrate was concentrated to yield a brown semi-solid. Trituration of this with diethyl ether–hexane (1:1) provided a gum that when stirred with methanol solidified. This yellow solid (1.17 g), a mixture of **11** and the desired product **20** (3:2 by ^1H NMR), was boiled with ethanol for 5 min and then filtered whilst hot to afford the product 2-(*morpholin*-4-*yl*)-4-(4-*nitrophenyl*)-5-*oxo*-4H-*indeno*[1,2-b]*pyran*-3-*carbonitrile* **20** as a grossly insoluble, bright-yellow solid (457 mg, 11%). Spectral and microanalytical parameters are shown in Tables 2 and 3.

The carbonitrile **21** was prepared in the same manner with a final clean-up by flash chromatography on grade 3 neutral alumina with ethyl acetate–hexane (1:2) as eluent rather than by boiling with ethanol.

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