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Articles

Synthetic Routes to Quinoline Derivatives: Novel Syntheses of 3-Butyryl-8-methoxy-4-[(2-methylphenyl)amino]quinoline and 3-Butyryl-8-(2-hydroxyethoxy)-4-[(2-methylphenyl)amino]quinoline

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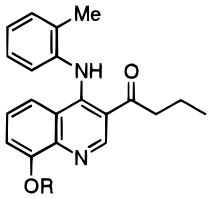
Abstract:

The 3,4,8-trisubstituted quinoline derivatives 2-butyryl-8-methoxy-4-[(2-methylphenyl)amino]quinoline and 3-butyryl-8-(2-hydroxyethoxy)-4-[(2-methylphenyl)amino]quinoline were prepared using five novel synthetic strategies, each involving a different disconnection as a basis for the key step. One such strategy led to the development of highly efficient processes for the large-scale preparations of both compounds and featured a facile cyclisation of an [(arylamino)methylene]malonate and an unusual Reformatsky reaction of a quinoline-3-carboxylate with *tert*-butyl 2-bromobutyrate in the presence of zinc.

Introduction

The 3,4,8-trisubstituted quinoline derivatives 3-butyryl-8-methoxy-4-[(2-methylphenyl)amino]quinoline (**1a**) and 3-butyryl-8-(2-hydroxyethoxy)-4-[(2-methylphenyl)amino]-quinoline (**1b**) emerged from SmithKline Beecham's gastrointestinal research programme as reversible (H^+/K^+) ATPase inhibitors for the treatment of peptic ulcers, gastro-oesophageal reflux disease, and related disorders and have been described previously.[1−3] This paper summarises exploratory work on a number of alternative routes to these compounds and describes how one route was developed into a viable commercial synthesis. Each of the five general strategies explored featured one of the disconnections a−e shown in Figure 1 as a basis for the critical conversions. Furthermore an efficient process for the conversion of **1a** to **1b** was developed.



1a : R = Me
1b : R = CH_2CH_2OH
1c : R = H

Results and Discussion

Disconnection a: C_4−Ring Junction. Much of the earlier work performed on **1a** and **1b** was based on this disconnection. The compounds were originally prepared within the Medicinal Chemistry research programme using several routes, the most promising one of which is shown in Scheme 1.[1,2] Although this classical route was amenable to the large-scale preparation of **1a**, the requirement for either aluminium trichloride or boron tribromide for the demethylation of the 8-methoxyquinoline **4a** to give the somewhat unstable 8-hydroxy analogue **4b** and poor yields for the alkylation of the latter to give the final product **1b** necessitated the acquisition of alternative methodology for the preparation of **1b**. The aspects concerning the evolution of an efficient conversion of **1a** to **1b** are dealt with later in the paper.

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(1) Ife, R. J.; Brown, T. H.; Keeling, D. J.; Leach, C. A.; Meeson, M. L.; Parsons, M. E.; Reavill, D. R.; Theobald, C. J.; Wiggall, K. J. *J. Med. Chem.* **1992**, *35*, 3413.
(2) Leach, C. A.; Brown, T. H.; Ife, R. J.; Keeling, D. J.; Parsons, M. E.; Theobald, C. J.; Wiggall, K. J. *J. Med. Chem.* **1995**, *38*, 2748.
(3) Andrews, I. P.; Bannister, R.; Etridge, S. K.; Lewis, N. J.; Mullane, M. V.; Wells, A. S. *Tetrahedron Lett.* **1995**, *36*, 7743.

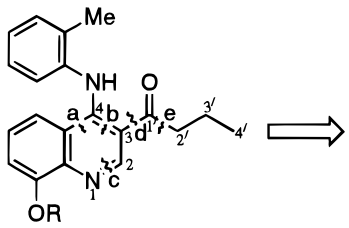
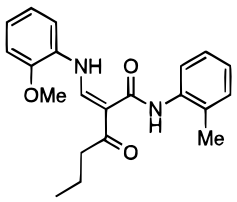


Figure 1. **Various disconnections of 1a/b.**

The chemistry outlined in Scheme 1 enabled the preparation of multikilogram quantities of **1a** within the pilot plant, thereby funding our early drug development studies. However, the route incorporated the Conrad−Limpach cyclisation reaction[4] of the α-keto acrylate **2**, requiring a temperature of ∼255 °C in a high-boiling solvent such as diphenyl ether or *tert*-butyldiglyme, conditions which on a commercial scale are expensive and require specialised equipment. It was therefore considered essential to discover more viable synthetic routes to both **1a** and **1b**.

To this end, another group within our laboratories had developed an efficient method for the preparation of **1a** based on the same disconnection by the cyclisation of the acrylamide **5** using $Ph_3P/C_2Cl_6/Et_3N$ at 110−120 °C.[3] It was nevertheless considered expedient to discover and screen as many strategically new routes to **1a** (and therefore **1b**) as possible, with a view to finding the most efficient and cost effective processes to these compounds.



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Disconnection b: C3−C4. Disconnection b in structure **1** provided the basis for a route proceeding via a vinylogous amide **8** (Scheme 2).The keto aldehyde[5] **7** was prepared as shown using the method of Price and Pappalardo.[6] Reaction of 1-chlorohexen-3-one[7] (**9**) with methanolic sodium hydroxide gave an intermediate acetal, which with *in situ* acid-catalysed hydrolysis afforded the β-ketoaldehyde **7**, which was used immediately for reaction with methyl 3-methoxyanthranilate[8] (**6**) to give the vinylogous amide **8** in 92% yield. Reaction of amide **8** with sodium ethoxide in ethanol resulted in ring closure to give the 4-quinolone **3** in 64% yield. The latter could be converted to **1a** in the manner described earlier. The formation of vinylogous amides of this nature from the Michael addition of anilines to acetylenic ketones and their subsequent conversion to 3-acyl-4-quinolones has been described previously.[9] Although this process clearly avoided the need for a high-temperature cyclisation, it nevertheless suffered from the disadvantage of starting from the prohibitively expensive trisubstituted benzene derivative **6**.

Disconnection c: N1−C2. A consideration of disconnection c in structure **1** led to the discovery of a novel route featuring a β-diketone intermediate **11** (Scheme 3). Treatment of methyl 3-methoxy-2-nitrobenzoate (**10**) with the anion of 2-pentanone gave a 56% yield of the β-diketone **11a**, which was shown by ^{1}H NMR to exist solely in the enol form **11b** in solution. Condensation of the latter with DMF dimethyl acetal afforded the nitro enamine **12** in 55% yield, which in turn was subjected to hydrogenation conditions over palladium-on-carbon to give the 4-quinolone **3** in 95% yield. The latter conversion presumably proceeded via an amino enamine intermediate which underwent spontaneous cyclisation to give the quinolone **3**.

In common with the previously discussed vinylogous amide approach this route possessed the advantage of avoiding a high-temperature cyclisation but again had the disadvantage of utilising a highly expensive trisubstituted benzene derivative, **10**, as starting material.

Disconnection d: C3−C1′. Introduction of the butyryl substituent via functionalisation at the 3-position of the quinoline nucleus was the essential feature in this novel approach to the target molecules (Scheme 4).

The 4-(arylamino)quinoline **14a** was prepared from 8-methoxy-4-quinolone (**13**) using established chemistry.[1,10] With somewhat surprising exclusivity, bromination at the electron-rich 3-position was achieved by treatment with NBS in refluxing carbon tetrachloride, giving the bromoquinoline **14b** in 95% yield. Formation of the intermediate lithio derivative **14c** was carried out via lithium−halogen exchange on the bromoquinoline **14b** using *n*-butyllithium in THF at −70 °C, and the former was quenched *in situ* by treatment with *N*-methoxy-*N*-methylbutyramide[11] (**15a**) to give **1a** in 66% yield.

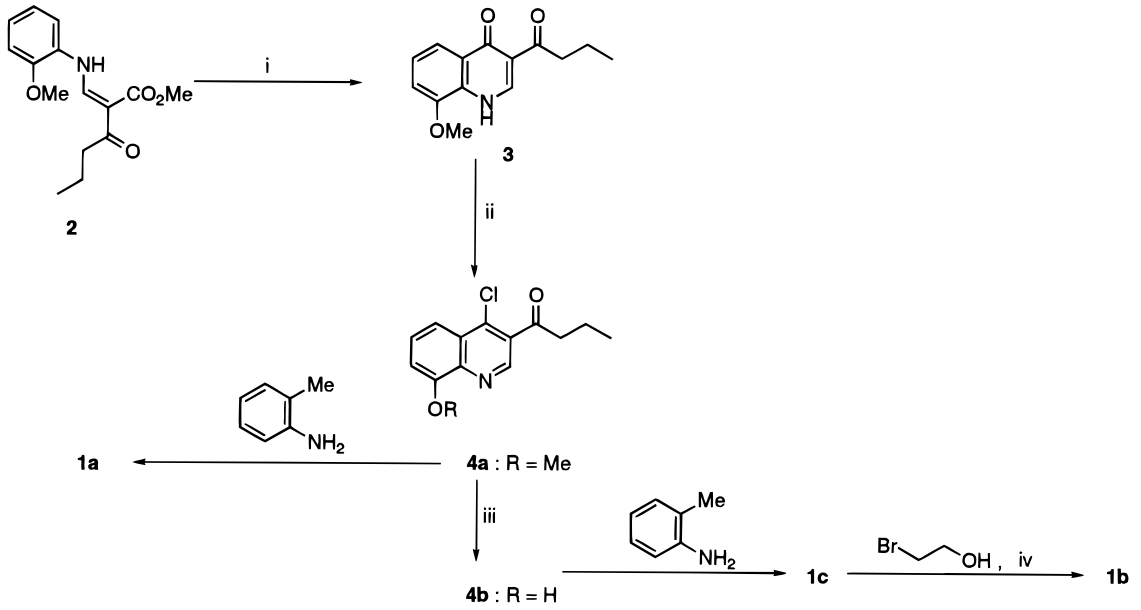
The conversion was also achieved using the cheaper *N*,*N*-dimethylbutyramide (**15b**), which afforded a similar yield of the desired product **1a**. Using this methodology it ought to be possible to prepare a wide variety of 3-substituted quinoline derivatives by quenching the anion **14c** with different electrophiles. Although this route appears attractive from a number of standpoints, it nevertheless included the classical high-temperature Conrad−Limpach cyclisation for the preparation of the intermediate **13**.[4]

Disconnection e: C1′−C2′. Schemes 5−7 show three routes to **1a**, each proceeding via a relatively low temperature cyclisation of the malonate derivative **18** and with the key step for each one being the conversion of a quinoline-3-carboxylic acid derivative to the desired aralkyl ketone using Grignard chemistry.

The common intermediate, the [(arylamino)methylene]-malonate[10] **18**, was formed by condensation of 2-anisidine

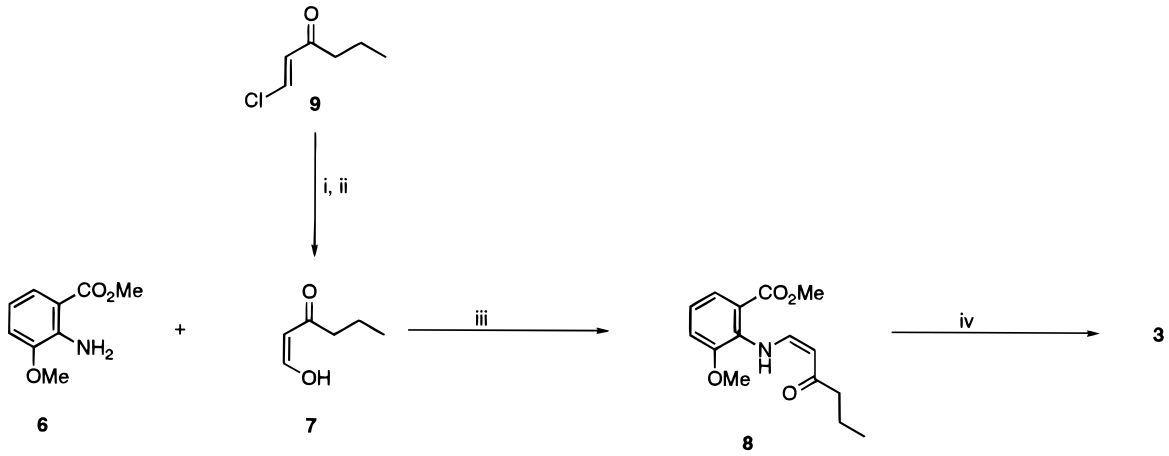
(4) Conrad, M.; Limpach, L. *Chem. Ber.* **1887**, *20*, 944.
(5) Winter, M. *Helv. Chim. Acta* **1963**, *46*, 1749.
(6) Price, C. C.; Pappalardo, J.A. *Organic Syntheses*; Wiley: New York, 1963; Collect Vol. IV; p 558.
(7) Opitz, G.; Zimmermann, F. *Justus Liebigs Ann. Chem.* **1963**, *662*, 178.
(8) Ramesh, M.; Shanmugam, P. *Indian J. Chem., Sect. B* **1985**, *24*, 602.
(9) Sinsky, M.S.; Bass, R.G. *J. Heterocycl. Chem.* **1984**, *21*, 759.
(10) Lauer, W. M.; Arnold, R. T.; Tiffany, B.; Tinker, J. *J. Am. Chem. Soc.* **1946**, *68*, 1268.
(11) Nahm, S.; Weinreb, S.M. *Tetrahedron Lett.* **1981**, *22*, 3815.

Scheme 1[a]



[a] Reagents: i, Ph_2O, 255 °C; ii, $POCl_3$, 100 °C; iii, $AlCl_3$ or BBr_3; iv, KO-*t*-Bu.

Scheme 2[a]



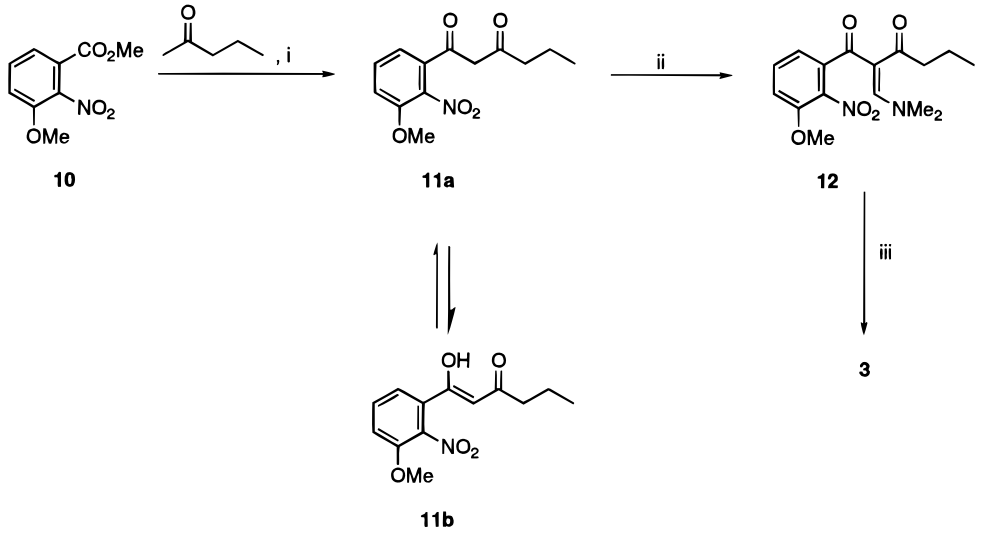
[a] Reagents: i, NaOH, MeOH; ii, HCl; iii, neat, −15 °C; iv, NaOEt, EtOH.

(**16**) with the commercially available diethyl (ethoxymethylene)malonate (**17**). Scheme 5 shows one route in which the malonate **18** was cyclised to give the chloroquinoline ester[12] **19** in 58% yield using the method of Nakagome's group,[13] *viz.*, by heating in phosphorus oxychloride at 100 °C. Reaction of the ester **19** with 2-toluidine gave the known amino ester[12] **20** in 70% yield, which in turn was converted to **1a** in 7.3% yield by treatment with propylmagnesium chloride in diethyl ether/THF at −70 °C. The yield of **1a** obtained from this reaction was limited to a large extent by the formation of the tertiary alcohol **24** as a by-product. A yield improvement to 58% and reduced formation of tertiary alcohol **24** resulted from the premixing of the ester **20** with 2 equiv of LDA prior to reaction with the Grignard reagent due presumably to the protection of the initially formed ketone **1a** as its enolate.[14]

In an alternative route, shown in Scheme 6, the malonate derivative **18** was cyclised to a ∼1:1 mixture of the 4-quinolone ester **21a** and its derived carboxylic acid **21b** in ∼60% yield by heating in a mixture of PPA and phosphorus oxychloride at 100 °C.[15] Treatment of the ester/acid mixture **21a**/**21b** with aqueous methanolic sodium hydroxide afforded solely the 4-quinolonecarboxylic acid[10] **21b**, which in turn was reacted with thionyl chloride to give the chloro acid chloride[1] **22a** in 89% yield. The acid chloride **22a** was converted to the chloro ketone **4a** in 26% yield by reaction with propylmagnesium chloride in diethyl ether/THF. The ketone **4a** was a key intermediate in the original syntheses of **1a** and **1b**. Use of excess propylmagnesium chloride led to a much poorer yield of chloro ketone **4a** due to the predominance of side reactions which afforded the ring-alkylated derivative **25** and the secondary alcohol **26**, the latter being formed as a result of β-hydride ion transfer to the initially formed ketone **4a** from unreacted Grignard

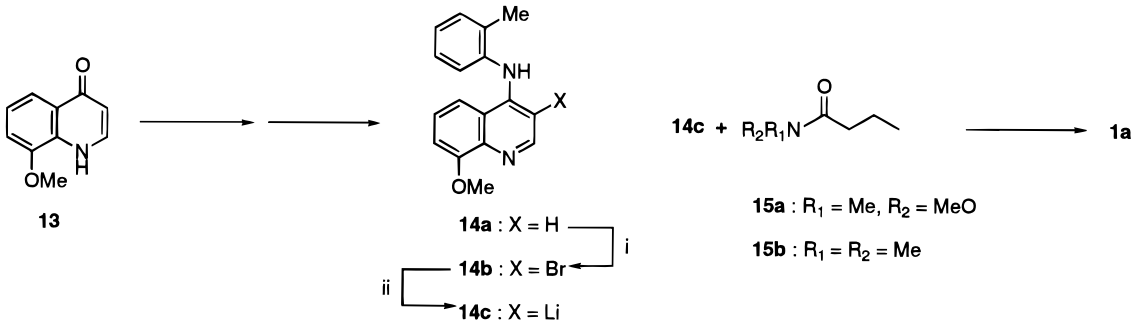
(12) Munson, H.R., Jr.; Alphin, R.S. US Patent 4 343 804; *Chem. Abstr.* **1983**, *98*, 143284.
(13) Agui, H.; Mitani, T.; Nakashita, M.; Nakagome, T. *J. Heterocycl. Chem.* **1971**, *8*, 357.
(14) Fehr, C.; Galindo, J. *Helv. Chim. Acta.* **1986**, *69*, 228
(15) Kametani, T.; Kigasawa, K.; Hiiragi, M.; Wakisaka, K.; Kusama, O.; Sugi, H.; Kawasaki, K. *J. Heterocycl. Chem.* **1977**, *14*, 1175.

Scheme 3[a]



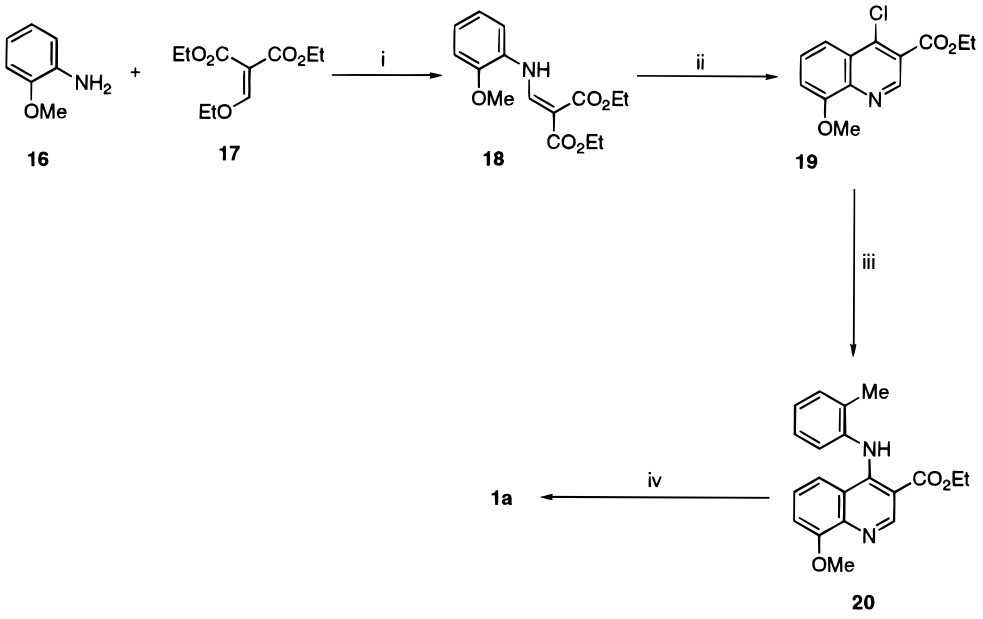
[a] Reagents: i, LDA; ii, DMF-DMA; iii, H_2, Pd−C.

Scheme 4[a]



[a] Reagents: i, NBS; ii, *n*-BuLi, −70 °C.

Scheme 5[a]



[a] Reagents: i, toluene, 100 °C; ii, $POCl_3$, 100 °C; iii, 2-Me(C_6H_4)NH_2; iv, PrMgCl, THF.

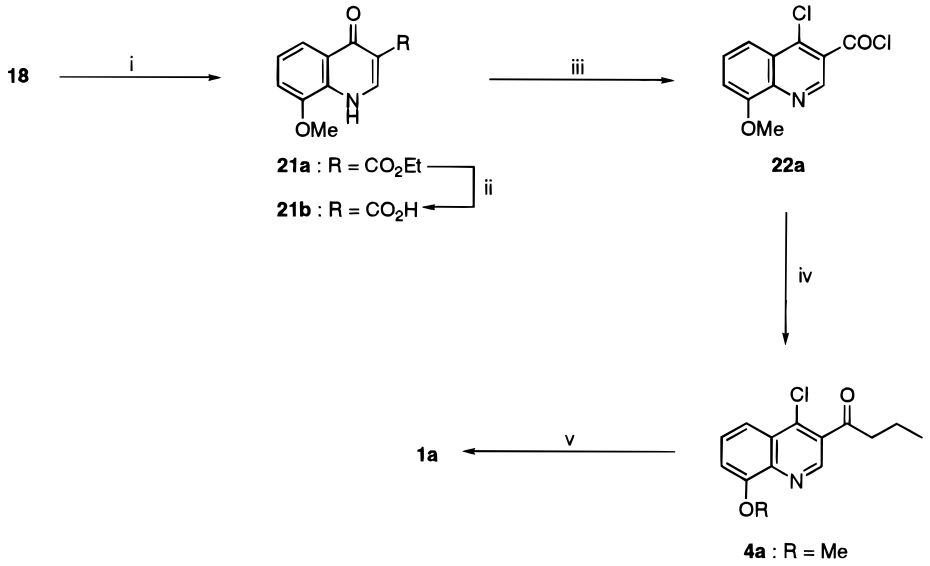
reagent. A range of catalysts were evaluated for this conversion including $Fe(acac)_3$[16] and Cu−CuCl,[17] but no improvements were obtained and in many cases enhanced amounts of the ring-alkylated compound **25** were formed.

The chloro acid chloride **22a** was also converted to the chloro amide **22b** in 70% yield by reaction with dimethyl-

(16) Fiandanese, V.; Marchese, G.; Martina, V.; Ronzini, L. *Tetrahedron Lett.* **1984**, *25*, 4805. Cardellicchio, C.; Fiandanese, V.; Marchese, G.; Ronzini, L. *Tetrahedron Lett.* **1987**, *28*, 2053.

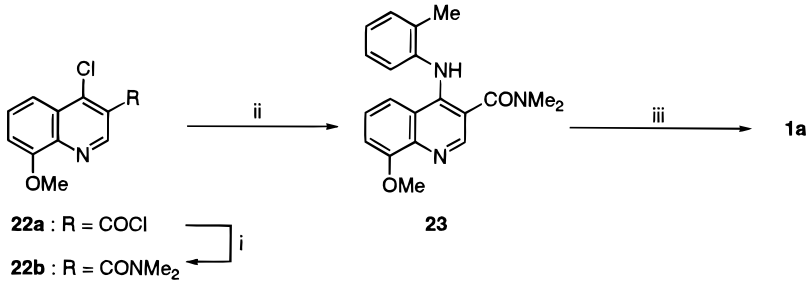
(17) Kuo, D.L. EP 446 872; *Chem. Abstr.* **1991**, *115*, 256014.

Scheme 6[a]

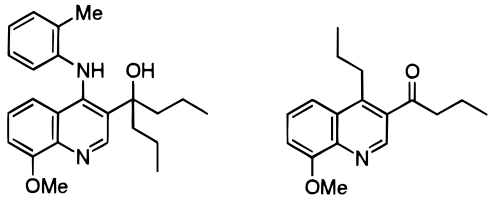


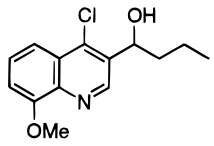
[a] Reagents: i, $POCl_3$−PPA, 100 °C; ii, NaOH, MeOH; iii, $SOCl_2$, DMF; iv, PrMgCl, THF; v, 2-Me(C_6H_4)NH_2.

Scheme 7[a]



[a] Reagents: i, Me_2NH·HCl, C_5H_5N; ii, 2-Me(C_6H_4)NH_2; iii, PrMgCl, THF.





amine hydrochloride in the presence of pyridine, as shown in Scheme 7. Treatment of the chloro amide **22b** with 2-toluidine afforded the amino amide **23** in 48% yield, which in turn on treatment with propylmagnesium chloride gave **1a** in 18% yield.

Although the conversion of the malonate derivative **18** to either the chloro ester **19** or the 4-quinolone ester **21a** could be conducted at relatively low temperatures (100 °C), thereby satisfying the requirement for facile C_4−ring junction bond formation based on disconnection a,[18] all three routes outlined above suffered from the serious disadvantage of very low yields for the Grignard reactions.

Evolution of the general strategy illustrated in Schemes 5−7 led to the discovery of a new and highly efficient "two-pot" synthesis of **1a** from inexpensive, readily available starting materials as shown in Scheme 8.

The previously discussed conversion of 2-anisidine (**16**) to the quinoline ester **20** was eventually achieved without isolation of intermediates and without inconvenient solvent changes. 2-Anisidine (**16**) and diethyl (ethoxymethylene)-malonate (**17**) were heated in refluxing butyl acetate, and the resulting solution of the [(arylamino)methylene]malonate **18** was added dropwise to a mixture of polyphosphoric acid trimethylsilyl ester (PPSE)[19] and phosphorus oxychloride in butyl acetate at 70 °C. The resulting solution of the chloroquinoline **19** was treated with 2-toluidine below 100 °C to give the amino ester **20** in 70% yield after work-up.

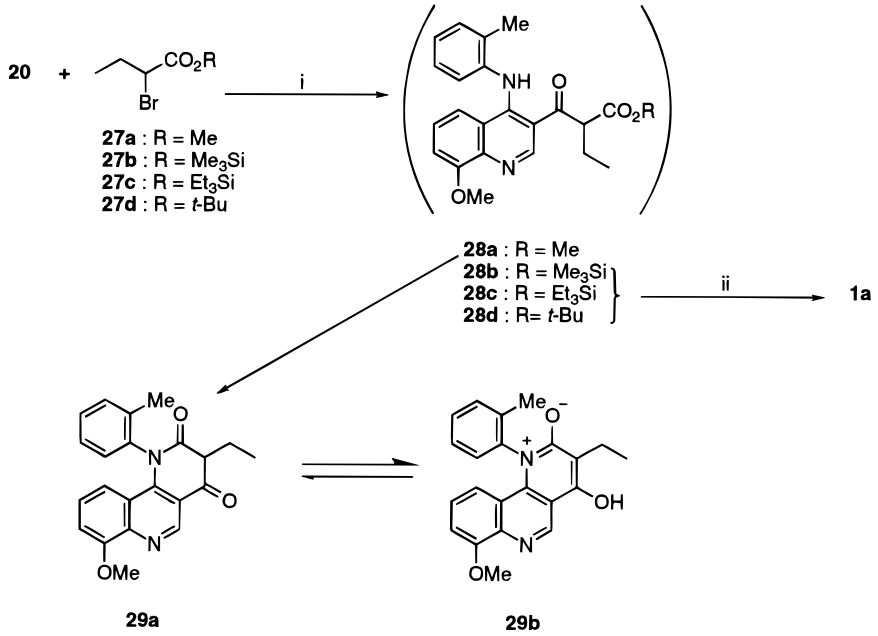
It was envisaged that the keto ester **28** might be obtainable via a Claisen condensation, particularly since ethyl pyridine-3-carboxylate had been reported to undergo such reactions.[20] However, no condensation between the quinoline **20** and methyl butyrate could be induced despite the screening of a wide variety of bases. It was subsequently discovered,

(18) It should be noted that these conditions are inappropriate for the preparation of 3-acyl-4-quinolones. Attempted cyclisations of the α-keto acrylate **2** in the presence of acidic dehydrating agents such as PPA or $POCl_3$ resulted in very poor yields of quinolone **3** and were accompanied by extensive side reactions.

(19) Flouzat, C.; Guillaumet, G. *J. Heterocycl. Chem.* **1991**, *28*, 899.

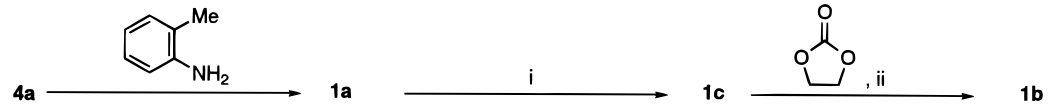
(20) Shivers, J. C.; Dillon, M. L.; Hauser, C. R. *J. Am. Chem. Soc.* **1947**, *69*, 119.

Scheme 8[a]



[a] Reagents: i, Zn, THF; ii, see text.

Scheme 9[a]



[a] Reagents: i, LiBr/LiI·xH$_2$O, 2,4,6-collidine; ii, DABCO.

somewhat surprisingly, that Reformatsky reactions between the quinoline ester **20** and the 2-bromobutyrates **27a**−**d** in the presence of activated zinc could be effected. Two possible explanations for the reactivity of ester **20** towards the Reformatsky reagents derived from the bromo esters **27a**−**d** are (i) that hydrogen bonding between the N−H proton and the carbonyl moiety of the ester renders the latter more electron deficient and therefore more reactive towards carbanions, and (ii) that chelation of zinc between the aliphatic nitrogen and the carbonyl oxygen allows stabilisation of intermediates derived from the reaction of the ester **20** and the Reformatsky reactants. The previously shown lack of participation of the ester **20** in Claisen reactions gave the latter explanation more credence. In the case of methyl 2-bromobutyrate (**27a**) the corresponding intermediate Reformatsky product **28a** could not be isolated and failed to undergo hydrolysis to **1a**, instead undergoing intramolecular lactam formation to give the novel tricyclic compound **29a**, which was found to be completely resistant to hydrolysis by either acids or bases. The lactam **29a** was shown by ^{1}H and ^{13}C NMR to exist in solution as the fully aromatised betaine **29b**.

When ester **20** was reacted with silyl esters **27b** and **27c** under Reformatsky conditions, the resulting intermediate keto esters **28b** and **28c** underwent hydrolysis followed by spontaneous decarboxylation during work-up to give acceptable yields of **1a**. Unfortunately, vast excesses of reagents were necessary since, even with 10 equiv each of activated zinc and the bromo ester **27b**, up to 20% of starting ester **20** was observed in the reaction mixture.

However, gratifyingly when ∼5 equiv each of *tert*-butyl 2-bromobutyrate[21] (**27d**) and activated zinc[22] was used, the Reformatsky reaction reached completion, thereby enabling isolation of the keto ester **28d** as a crude intermediate in excellent yield. The crude keto ester **28d** was found to undergo hydrolysis and decarboxylation by heating in formic acid at 100 °C to give **1a** with an overall yield of 73% from the quinoline ester **20**. Initial problems with product contamination by zinc hydroxide were overcome by using 6 M NaOH washes. Although the conversion of the quinoline ester **20** to **1a** could be readily accomplished as a one-pot process, it was nevertheless found possible to isolate and characterise pure keto ester **28d**.

Thus we had developed an extremely concise route to **1a**, and having completed our alternative route explorations, we selected and successfully piloted, on the 50 gal scale, the malonate-Reformatsky chemistry described above.

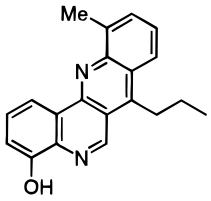
Conversion of 1a to 1b: Dealkylation−Alkylation Studies. Our first approach to address the problem of the refunctionalisation of the 8-oxygen substituent was to develop a sequence very similar to that shown earlier, in Scheme 1, the main difference being the order of the functional group manipulations (Scheme 9). Thus the demethylation step was performed following arylamination thereby avoiding both the troublesome dealkylation of the chloromethoxyquinoline **4a** and the isolation of the resulting

(21) Shin, C.; Nanjo, K.; Ando, E.; Yoshimura, J. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 3109.

(22) It was later found that zinc could be activated *in situ* by heating the metal powder in refluxing THF, containing 1−2 mol % glacial acetic acid, for a short period prior to the addition of the quinoline ester **20**.

unstable chlorohydroxyquinoline **4b** of the earlier process.

Demethylation of **1a** was readily achieved by heating in the presence of HCl or HBr, but the yields were always compromised by the formation of significant quantities of the tetracyclic compound **30**, from which the hydroxyquinoline **1c** could not be readily separated. The tetracycle **30** presumably arose from an intramolecular Friedel−Crafts reaction and could be isolated in 83% yield by heating of the hydroxyquinoline **1c** in refluxing concentrated aqueous HCl.



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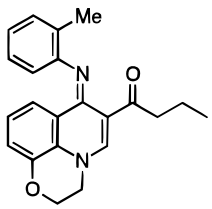

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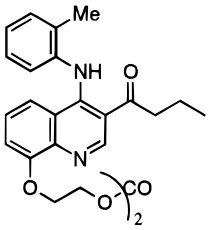

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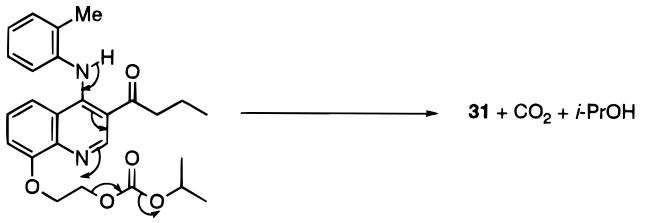
A more efficient demethylation of **1a** was obtained by using 1.5 equiv of hydrated lithium iodide in 2,4,6-collidine at 150 °C, giving yields of 80−85% with no detectable amounts of the tetracycle **30**. It was subsequently found that the relatively high cost of lithium iodide could be offset by using the much cheaper lithium bromide (1.5 equiv) in association with only 0.15 equiv of the hydrated iodide, this mixture giving yields similar to those obtained by using the iodide alone, in collidine.

The final hydroxyethylation stage to form **1b** was previously performed by using 2-bromoethanol in the presence of potassium *tert*-butoxide, giving yields of ∼30%.[2] Extensive development work facilitated the evolution of a superior process, which involved the use of ethylene carbonate in the presence of either K_2CO_3 or DABCO in refluxing 2-propanol and afforded **1b** in 60−80% yield. The main drawback with these methods, however, was the consistent formation of the tricyclic compound **31**, which emerged as an impurity in the final product at levels of ∼8%. Very small amounts of two other by-products, the symmetrical carbonate **32** and the isopropyl carbonate **33**, were also observed. The symmetrical carbonate **32** impurity was fortuitously converted to **1b** thermolytically during the preparation of the pharmaceutically presentable hydrochloride salt, which involved heating in a solution of HCl in 2-propanol. The tricyclic compound **31** and the symmetrical carbonate **32** were isolated by chromatography of **1b** crystallisation mother liquors and of crude **1b**, respectively, whereas the isopropyl carbonate **33** was characterised on the basis of LCMS studies.

A substantial improvement in the alkylation process was obtained by replacement of 2-propanol by *tert*-butyl alcohol,

Scheme 10



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which effectively avoided the formation of both by-products **31** and **33**, giving **1b** in 97% yield and with a considerably reduced reaction time. Presumably formation of the *tert*-butyl analogue of **33** was disfavoured on steric and electronic grounds, although the reduced reaction time may also have been a significant factor. Since the isopropyl carbonate **33** was a likely intermediate in the formation of the tricycle **31** in 2-propanol (Scheme 10), the absence of the *tert*-butyl analogue of **33** would account for the suppression of the latter's formation in *tert*-butyl alcohol. In fact extremely low levels of the symmetrical carbonate **32** and the tricycle **31** were detected in the reaction liquors but they failed to interfere with the isolation of highly pure **1b** from *tert*-butyl alcohol.

We had therefore realised our ambition to discover and develop a commercially viable route not only to **1a** but also to **1b**. Unfortunately, the applicability of the efficient conversion of **1a** to **1b** described above to the pilot-plant scale could not be evaluated owing to the termination of the SK&F-96067/SK&F-97574 projects.

Conclusions

A number of new synthetic routes to **1a** and **1b** were discovered. One such route fully satisfied our aim of developing a convenient high-yielding process which, unlike most of the earlier approaches, avoided the need for a high-temperature ring closure to form the quinoline nucleus. The pivotal stages for this route were a facile cyclisation of a malonate derivative **18** and a Reformatsky reaction on the derived quinoline ester **20** using *tert*-butyl 2-bromobutyrate **27d** in the presence of zinc.

Experimental Section

Melting points were measured with a Büchi 510 melting point apparatus and are uncorrected. Elemental analyses were performed using a CEC 440 instrument. IR spectra were recorded on either a Perkin-Elmer 781 or a Nicolet 710 FT-IR spectrophotometer. ^{1}H (270 MHz) and ^{13}C (62.5 MHz) NMR spectra were recorded on a Jeol JNH-GX 270 FT spectrometer, while ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR spectra were recorded on a Jeol GSX-400 FT spectrometer, using solutions in $CDCl_3$ unless otherwise stated. Chemical shifts are reported as parts per million downfield from tetramethylsilane as internal standard, and coupling constants *J* are given in hertz. CI, EI, and FAB mass spectra were recorded on a VG TRIO-2 mass spectrometer, while FIA (electrospray flow injection analysis) spectra and LCMS were recorded on a SCIEX API-III instrument. Accurate mass measurements were performed on a VG 70-VSEQ spectrometer.

HPLC analyses were performed using a Beckman Gold 126 pump and 166 detector with a Kromasil C_{18} (5 μm) 250 × 4.6 mm column, eluting with mixtures of MeOH, THF, and 0.1% aqueous TFA and detecting at 254 nm. HPLC quantified yields were calculated with respect to authentic standards. Preparative chromatography was conducted using Ubichem silica gel 32−63 μ (technical). Ether refers to diethyl ether. All organic extracts were dried over $MgSO_4$, filtered, and concentrated using a Büchi rotary film evaporator.

3-Butyryl-8-methoxy-4-quinolone (3) (via Vinylogous Amide 8). A solution of 1-chloro-1-hexene-3-one (**9**)[7] (5 g, 37.7 mmol) in MeOH (10 cm^3) was cooled to ∼−10 °C and treated with a solution of NaOH (1.51 g, 37.8 mmol) in MeOH (20 cm^3) added dropwise over 1 h. The reaction mixture was stirred at −10 °C for a further 2 h and the resulting dark red solution poured into chilled brine (30 cm^3) and extracted with CH_2Cl_2 (2 × 30 cm^3). The organic extract was washed with HCl (1 M, 15 cm^3) and subsequently stirred at ambient temperature with aqueous HCl (50%, 30 cm^3) for 3 h. The CH_2Cl_2 solution was separated, dried and evaporated to give the intermediate β-keto aldehyde[5] **7** as a pale brown oil (4 g), to which was immediately added methyl 3-methoxyanthranilate[8] (**6**) (0.5 g, 2.8 mmol). The mixture was stored at −18 °C for 3 days. After being allowed to revert to ambient temperature, the mixture turned dark red due to decomposition of excess 3-oxohexanal enol. The crude product was chromatographed on silica gel using 3:1 60-80 petroleum/acetone as eluent to give **methyl 3-methoxy-2-[(3-oxo-1-hexenyl)amino]benzoate (8)** (0.71 g, 97%) as a red oil: ν_{max} (film)/cm^{-1} 3220 (NH), 1715 (CO_2Me), 1705 (C═O), 1635 (C═C), 1580 (Ar), and 1570 (Ar); δ_H (270 MHz) 0.95 (3H, t, *J* 7.5, C*H*$_3$CH$_2$CH$_2$CO), 1.70 (2H, sextet, *J* 7.5, CH$_3$C*H*$_2$CH$_2$CO), 2.40 (2H, t, *J* 7.5, CH$_3$CH$_2$C*H*$_2$CO), 3.85 (3H, s, CO_2CH_3), 3.98 (3H, s, $ArOCH_3$), 5.25 (1H, d, *J* 7.7, 2′-H), 6.92−7.14 (2H, m, Ar and 1′-H), 7.45−7.65 (2H, m, Ar), and 12.42 (1H, br d, *J* 11.6, N−H); *m*/*z* (EI) 277 (M^+, 66) and 234 ($M^+ - C_3H_7$, 88).

The vinylogous amide **8** (0.71 g, 2.56 mmol) was added to a solution of NaOEt in EtOH (20 cm^3 of 2.9 g of Na in 200 cm^3 of EtOH, 7.25 mmol) and the resulting solution heated under reflux for 15 min. The resulting suspension was allowed to cool and the EtOH removed *in vacuo* to give a residue, which was partitioned between EtOAc (30 cm^3) and HCl (1 M, 30 cm^3). The separated organic phase was dried and evaporated to give a dark orange solid, which was chromatographed on silica gel using 1:1 60−80 petroleum/acetone to give quinolone **3**[1] (0.4 g, 64%) as a pale yellow solid, mp 199−201 °C (lit.[1] mp 200−202 °C) identical to that reported previously.

1-(3-Methoxy-2-nitrophenyl)-1,3-hexanedione (11). To a freshly prepared solution of 2-pentanone (0.51 cm^3, 4.74 mmol) in dry THF (10 cm^3) containing LDA (9.48 mmol) at −78 °C under N_2 was added dropwise a solution of methyl 3-methoxy-2-nitrobenzoate (**10**) (1 g, 4.74 mmol) in dry THF (10 cm^3). The cooling was discontinued and the reaction mixture stirred for ∼2 h at ambient temperature. The resulting mixture was poured into water (20 cm^3) and extracted into CH_2Cl_2 (3 × 15 cm^3). The combined organic extracts were washed with water (10 cm^3) and concentrated *in vacuo* to give a greenish oil. Trituration with ether (20 cm^3) afforded, after drying, the diketone **11** (0.7 g, 56%) as a yellow solid: mp 62−64 °C dec (Found: MH^+ (EI), 266.1028. $C_{13}H_{16}NO_5$ requires *m*/*z* 266.1052); ν_{max} (KBr)/cm^{-1} 1600 (C═O), 1580 (Ar), and 1545 (NO_2); δ_H (400 MHz) 0.98 (3H, t, *J* 7.7, C*H*$_3$CH$_2$CH$_2$CO), 1.68 (2H, sextet, *J* 7.7, CH$_3$C*H*$_2$CH$_2$CO), 2.17 (1H, s, enol OH), 2.36 (2H, t, *J* 7.7, CH$_3$CH$_2$C*H*$_2$CO), 3.94 (3H, s, $ArOCH_3$), 5.97 (1H, s, enol CH), 7.17−7.29 (2H, m, Ar), and 7.45−7.53 (1H, m, Ar); δ_C (100 MHz) 13.6 (*C*H$_3$CH$_2$CH$_2$CO), 19.1 (CH$_3$*C*H$_2$-CH$_2$CO), 40.1 (CH$_3$CH$_2$*C*H$_2$CO), 56.7 ($ArOCH_3$), 98.2 [*C*H═C(OH)], 115.7-151.2 (6 C, Ar C), 183.5 [CH═*C*(OH)], and 194.7 (CH$_3$CH$_2$CH$_2$*C*O); *m*/*z* (CI) 283 (MNH_4^+, 100) and 266 (MH^+, 65); *m*/*z* (EI) 219 ($M^+ - NO_2$, 38), 194 ($M^+ - C_3H_7CO$, 7), 180 ($M^+ - C_3H_7COCH_2$, 33), 165 ($M^+ - C_3H_7COCH_2 - CH_3$, 9), 148 ($M^+ - C_3H_7CO - NO_2$, 27), and 119 ($M^+ - C_3H_7COCH_2 - NO_2 - CH_3$, 29).

Conversion of Diketone 11 to Quinolone 3. To a stirred solution of diketone **11** (0.4 g, 1.5 mmol) in toluene (2 cm^3) was added DMF dimethyl acetal (0.24 cm^3, 1.8 mmol), and the mixture was heated at 80 °C for 1.5 h. Water (10 cm^3) was added and the mixture extracted into CH_2Cl_2 (3 × 5 cm^3). The combined organic extracts were dried, concentrated and chromatographed on silica gel eluting with EtOAc to give **2-[(*N*,*N*-dimethylamino)methylene]-1-(3-methoxy-2-nitrophenyl)-1,3-hexanedione (12)** (0.27 g, 56%) as a yellow oil: δ_H (270 MHz) 0.84 (3H, t, *J* 7.5, C*H*$_3$CH$_2$CH$_2$-CO), 1.56 (2H, sextet, *J* 7.5, CH$_3$C*H*$_2$CH$_2$CO), 2.48 (2H, t, *J* 7.5, CH$_3$CH$_2$C*H*$_2$CO), 2.77 [3H, br s, (*E*)-N$^+$CH$_3$], 3.24 [3H, br s, (*Z*)-N$^+$CH$_3$], 3.95 (3H, s, $ArOCH_3$), 7.10−7.18 (2H, m, Ar), and 7.42−7.50 (1H, m, Ar); *m*/*z* (CI) 321 (MH^+, 100), 246 [$MH^+ - N(CH_3)_2 - OCH_3$, 27], and 234 ($MH^+ - CH_3CH_2CH_2CH(OH)CH_2$, 58); *m*/*z* (EI) 321 (MH^+, 2), 274 ($M^+ - NO_2$, 3), and 249 ($M^+ - CH_3CH_2CH_2CO$, 10).

A stirred solution of the enamine **12** (0.14 g, 0.44 mmol) in EtOH (5 cm^3) was hydrogenated over Pd/C (10%, 17 mg) under balloon pressure of hydrogen for 3 h. The catalyst was removed by filtration and the solution evaporated to dryness to give the **quinolone 3**[1] (0.102 g, 95%) as a paleyellow solid, shown by NMR to be identical to the sample prepared above.

3-Bromo-8-methoxy-4-[(2-methylphenyl)amino]quinoline (14b). NBS (6.5 g, 36.5 mmol) was added to a stirred solution of the quinoline **14a**[1] (9.6 g, 36 mmol) in CCl_4 (350 cm^3) and the mixture heated under reflux for 1 h. After cooling, the succinimide was removed by filtration and the filtrate concentrated. The resulting crude product was chromatographed on silica gel, eluting with EtOAc to give a pale brown solid, which was crystallised from EtOAc/hexane to give the 3-bromoquinoline **14b** (11.8 g, 95%) as a white crystalline solid: mp 182−183 °C. (Found: C, 59.52; H, 4.50; N, 8.09. $C_{17}H_{15}BrN_2O$ requires C, 59.49; H, 4.41; N, 8.16); ν_{max} (Nujol mull)/cm^{-1} 3362 (NH), 1585 (Ar), 1556 (Ar) and 1261 (CO); δ_H (400 MHz) 2.42 (3H, s, $ArCH_3$), 4.07 (3H, s, $ArOCH_3$), 6.20 (1H, br s, NH), 6.55−6.60 (1H, m, Ar), 6.96−7.28 (6H, m, Ar), and 8.88 (1H, s, 2-H); δ_C (100 MHz) 18.0 ($ArCH_3$), 56.0 ($ArOCH_3$), 107.5−155.7 (15C, Ar C); *m*/*z* (FIA) 343 (MH^+, 95), 328 ($MH^+ - CH_3$, 58), and 313 ($MH^+ - CH_2O$, 100).

Conversion of Bromoquinoline 14b to 1a. A solution of the 3-bromoquinoline **14b** (0.172 g, 0.5 mmol) in THF (3 cm^3) was added over 5 min to a stirred solution of *n*-BuLi (0.4 cm^3 of a 2.5 M solution in hexane, 1 mmol) in THF (2.5 cm^3) at −70 °C under N_2. The mixture was stirred at −70 °C for 15 min and treated with *N*-methoxy-*N*-methylbutyramide (**15a**)[11] (0.065 g, 0.5 mmol) in THF (1 cm^3). The solution was stirred at −70 °C for 30 min and allowed to warm to 0 °C over 15 min. Saturated NH_4Cl solution (2 cm^3) was added with vigorous stirring and the mixture separated. The organic phase was washed with water (2 cm^3), dried, concentrated *in vacuo*, and chromatographed on silica gel, eluting with EtOAc to give a yellow solid, which was recrystallised from EtOAc/hexane to give **1a**[1] (0.11 g, 66%) as yellow crystals: mp 111−113 °C (lit.[1] mp 112−114 °C); δ_H (400 MHz) 1.06 (3H, t, *J* 7.3, C*H*$_3$CH$_2$CH$_2$CO), 1.83 (2H, sextet, *J* 7.3, CH$_3$C*H*$_2$CH$_2$CO), 2.37 (3H, s, ArCH$_3$), 3.11 (2H, t, *J* 7.3, CH$_3$CH$_2$C*H*$_2$CO), 4.06 (3H, s, ArOCH$_3$), 6.89−6.92 (1H, m, Ar), 6.98−7.15 (5H, m, Ar), 7.28−7.31 (1H, m, Ar), 9.01 (1H, s, 2-H), and 11.82 (1H, br s, NH).

A repeat experiment using *N*,*N*-dimethylbutyramide **15b** (0.0575g, 0.5 mmol) gave **1a** (0.114 g, 68%) in a similar yield.

Diethyl [[(2-Methoxyphenyl)amino]methylene]malonate (18). Diethyl (ethoxymethylene)malonate (**17**) (5.41 g, 25 mmol) and 2-anisidine (**16**) (2.82 cm^3, 25 mmol) were mixed at ambient temperature, giving rise to an exotherm of 18 °C. Benzene (6.5 cm^3) was added and the resulting solution heated under reflux (83 °C) for 1.5 h. The solution was concentrated *in vacuo* to give an oil, which crystallised on standing. The crude product was slurried in hexane, filtered off, and air-dried to give the [(arylamino)methylene]malonate **18**[10] (6.43 g, 88%) as colourless crystals: mp 47−50 °C (lit.[10] mp 47.5−48.5 °C); δ_H (270 MHz) 1.38 (6H, 2t, *J* 7.0, C*H*$_3$-CH$_2$O), 4.30 (4H, 2q, *J* 7.0, CH$_3$C*H*$_2$O), 6.90−7.17 (2H, m, Ar), 7.24−7.30 (1H, m, Ar), 8.60 (1H, d, *J* 15.4, 2-H), and 11.15 (2H, br d, *J* 15.4, NH).

4-Chloro-3-(ethoxycarbonyl)-8-methoxyquinoline (19). A solution of diethyl [[(2-methoxyphenyl)amino]methylene]-malonate (**18**) (25 g, 85 mmol) in $POCl_3$ (125 cm^3, 1.34 mol) was heated under reflux for 18 h. The cooled solution was concentrated *in vacuo* and the resulting brown oil partitioned between CH_2Cl_2 (500 cm^3) and water (250 cm^3). The aqueous layer was separated, basified with NaOH (2 M, 100 cm^3) solution, and extracted into CH_2Cl_2 (100 cm^3). The combined organic extracts were dried and concentrated *in vacuo* to give a brown oil, which was chromatographed on silica gel eluting with 1:1 EtOAc/hexane followed by 9:1 EtOAc/MeOH to give as the main fraction the chloroester[12] **19** (13.2 g, 58%) as a pale oil, which crystallised to an off-white solid: mp 74−76 °C (lit.[12] mp 75−77 °C); δ_H (270 MHz) 1.47 (3H, t, *J* 7.0, C*H*$_3$CH$_2$O), 4.13 (3H, s, ArOCH$_3$), 4.51 (2H, q, *J* 7.0, CH$_3$C*H*$_2$O), 7.20 (1H,d, *J* 8.5, 7-H), 7.63 (1H, t, *J* 8.5, 6-H), 7.98 (1H, d, *J* 8.5, 5-H), and 9.19 (1H, s, 2-H).

3-(Ethoxycarbonyl)-8-methoxy-4-[(2-methylphenyl)-amino]quinoline (20). A solution of the chloroquinolone **19** (3.37 g, 12.7 mmol) and 2-toluidine (1.48 cm^3, 13.8 mmol) was heated in refluxing 1,4-dioxane (70 cm^3) for 2 h. The yellow solid which formed was removed by filtration of the hot suspension and taken up in CH_2Cl_2 (100 cm^3). The CH_2Cl_2 solution was washed with NaOH solution (2 M, 3 × 25 cm^3), dried, and concentrated *in vacuo* to give a solid, which was recrystallised from *i*-PrOH to give the 4-(arylamino)quinoline **20**[12] (3.0 g, 70%) as pale yellow crystals: mp 191−193 °C (lit.[1] mp 193−194 °C); δ_H (270 MHz) 1.47 (3H, t, *J* 7.1, C*H*$_3$CH$_2$O), 2.40 (3H, s, ArCH$_3$), 4.06 (3H, s, ArOCH$_3$), 4.43 (2H, t, *J* 7.1, CH$_3$C*H*$_2$O), 6.79−6.86 (1H, m, Ar), 6.97−7.14 (5H, m, Ar), 7.26−7.31 (1H, m, Ar), 9.29 (1H, s, 2-H), and 10.32 (1H, br s, NH).

Conversion of Ester 20 to 1a. Method A. To a stirred solution of the quinoline ester **20** (0.15 g, 0.45 mmol) in dry THF (5 cm^3) at 0 °C under N_2 was added a solution of PrMgCl (0.45 cm^3 of a 2 M solution in ether, 0.9 mmol) dropwise over 15 min. The resulting solution was stirred for a further 1 h at 0 °C and subsequently added dropwise to a chilled solution of HCl (1 M, 10 cm^3). CH_2Cl_2 (10 cm^3) was added and the stirred mixture basified with aqueous NaOH (2 M, 7.5 cm^3). The layers were separated and the aqueous solution re-extracted with CH_2Cl_2 (5 cm^3). The combined organic extracts were dried and concentrated *in vacuo* to give a brown oil, which was chromatographed on silica gel eluting with 9:1 EtOAc/MeOH to give **1a** (10.8 mg, 7.3%) as a yellow solid, identical to the compound prepared above on the basis of NMR and HPLC comparisons. Further elution afforded **3-(1-hydroxy-1-propylbutyl)-8-methoxy-4-[(2-methylphenyl)amino]quinoline (24)** (25 mg, 14.8%) as an off-white foam: ν_{max} ($CHCl_3$)/cm^{-1} 3600 (OH), 3320 (NH), and 1590 (Ar); δ_H (270 MHz) 0.62−2.37 [14H, complex multiplets, (C*H*$_3$C*H*$_2$C*H*$_2$)$_2$CH(OH)], 2.42 (3H, s, ArCH$_3$), 2.55 (1H, br s, OH), 4.06 (3H, s, ArOCH$_3$), 6.22−7.27 (7H, m, Ar), 8.47 (1H, s, 2-H), and 8.62 (1H, s, N-H); *m*/*z* (EI) 378 (M^+, 8), 360 ($M^+ - H_2O$, 100), 345 ($M^+ - H_2O - CH_3$, 17), 331 ($M^+ - H_2O - C_2H_5$, 52), and 317 ($M^+ - H_2O - C_3H_7$, 18).

Conversion of Ester 20 to 1a. Method B. Diisopropylamine (0.28 cm^3, 2.0 mmol) was added to a stirred solution of *n*-BuLi (0.79 cm^3 of a 2.5 M solution in hexane, 2.0 mmol) in THF (5 cm^3) at −10 °C under N_2. The resulting solution was stirred at −10 °C for 20 min before being cooled to −78 °C. The quinoline ester **20** (0.3 g, 0.89 mmol) was introduced in portions over 20 min, followed by PrMgCl (0.49 cm^3 of a 2 M solution in ether, 0.98 mmol) in THF (2 cm^3) added dropwise over 20 min. The solution was stirred for 2.75 h at −78 °C, the cooling discontinued, and the reaction mixture left stirring for 18 h at ambient temperature. The solvent was removed *in vacuo* and the residue treated with HCl solution (1 M, ∼10 cm^3). The resulting aqueous solution was basified with NaOH (2 M, 7.5 cm^3) solution and extracted into EtOAc (3 × 7.5 cm^3). The emulsion which formed was dispersed by the addition of a few drops of HCl (1 M) solution. The organic extracts were combined, dried, and evaporated to give a brown oil (0.34 g), HPLC analysis of which revealed the presence of **1a** (58%).

8-Methoxy-4-quinolone-3-carboxylic Acid (21b). The [(arylamino)methylene]malonate **18** (6 g, 20.5 mmol) was heated in $POCl_3$ (49 cm^3, 0.525 mol) containing PPA (23 g) at 100 °C with stirring for 1 h. After allowing the reaction mixture to cool to ambient temperature, the excess $POCl_3$

was decanted off and the resulting dark brown oil carefully treated with chilled water (50 cm^3). A considerable exotherm was observed due to the presence of residual $POCl_3$. The pH of the resulting suspension was adjusted to ~6 using NaOH (2 M) solution, and the mixture was stored at −14 °C for 20 h. The resulting solid was collected via suction filtration, washed with water and dried over P_2O_5 under reduced pressure to give the quinolone derivative **21** (3.14 g, ~60%) as a buff solid. NMR analysis revealed the product to be a ~1:1 mixture of ester **21a** and carboxylic acid **21b**.[10]

The ester/acid mixture **21a**/**21b** (3.14 g, ~12.5 mmol) was heated in a refluxing solution of NaOH (3.0 g, 75 mmol) in 1:1 EtOH/water (60 cm^3) for 6 h. The EtOH was removed *in vacuo* and the aqueous solution washed with EtOAc (30 cm^3). The pH of the aqueous solution was adjusted to ~5.5 using HCl (1 M) and the precipitated solid filtered off, washed with water, and dried over P_2O_5 under reduced pressure to give the carboxylic acid **21b**[10] (2.7 g, 91%) as a buff solid: mp 277−279 °C (lit.[10] mp 280 °C dec); δ_H (270 MHz; [$^2H_6$]DMSO) 3.28 (1H, br s, NH), 4.10 (3H, s, $ArOCH_3$), 7.42−7.60 (2H, m, Ar), 7.80−7.85 (1H, m, Ar), 8.57 (1H, s, 2-H), and 12.85 (1H, br s, CO_2H).

4-Chloro-8-methoxy-3-quinolinecarbonyl Chloride (22a). The carboxylic acid **21b** (2.7 g, 12.3 mmol) was heated in refluxing thionyl chloride (8 cm^3, 0.11 mol) containing DMF (2 drops) for 2.5 h. The solution was evaporated to dryness *in vacuo* to give a solid, which was triturated with ether, filtered off, and dried to give the acid chloride **22a**[1] (2.8 g, 89%) as an orange solid: mp 166−170 °C (lit.[1] mp 167−172 °C); δ_H (270 MHz) 4.23 (3H, s, $ArOCH_3$), 7.46 (1H, d, *J* 8.5, 7-H), 7.88 (1H, t, *J* 8.5, 6-H), 8.11 (1H, d, *J* 8.5, 5-H), and 9.63 (1H, s, 2-H).

Conversion of Acid Chloride 22a to 3-Butyryl-4-chloro-8-methoxyquinoline (4a). To a solution of the chloro acid chloride **22a** (0.5 g, 2 mmol) in dry THF (15 cm^3) at −65 °C under N_2 was added PrMgCl (1 cm^3 of a 2 M solution in THF, 2 mmol) dropwise over 20 min. The resulting dark brown reaction mixture was stirred at −60 °C for 30 min and subsequently partitioned between EtOAc (20 cm^3) and brine (50%, 15 cm^3). The aqueous layer was re-extracted with EtOAc (10 cm^3), and the combined organic phases were dried and evaporated to give a pale orange residue (0.45 g). The latter was chromatographed on silica gel (100 g) eluting with EtOAc to give the chloro ketone **4a**[1] (0.135 g, 26%) as a pale yellow oil, which crystallised on standing to give an off-white solid: mp 112−115 °C (lit.[1] mp 114−116 °C); δ_H (270 MHz) 0.97 (3H, t, *J* 7.7, $CH_3CH_2CH_2CO$), 1.74 (2H, sextet, *J* 7.7, $CH_3CH_2CH_2CO$), 2.98 (2H, t, *J* 7.7, $CH_3CH_2CH_2CO$), 4.04 (3H, s, $ArOCH_3$), 7.12 (1H, d, *J* 8.1, 7-H), 7.57 (1H, t, *J* 8.1, 6-H), 7.84 (1H, d, *J* 8.1, 5-H), and 8.80 (1H, s, 2-H).

A repeat experiment using a 2-fold excess of PrMgCl (2 cm^3 of a 2 M solution in ether) resulted in a much reduced yield of chloro ketone **4a** (46 mg, 9%) following chromatography. Further elution of the column resulted in the isolation of **3-butyryl-8-methoxy-4-propylquinoline (25)** (60mg, 11%) as a an off-white foam: δ_H (270 MHz) 1.00−1.14 (6H, m, $CH_3CH_2CH_2CO$ and $CH_3CH_2CH_2Ar$), 1.67−1.92 (4H, m, $CH_3CH_2CH_2CO$ and $CH_3CH_2CH_2Ar$), 2.98 (2H, t, *J* 7.7, $CH_3CH_2CH_2CO$), 3.10−3.28 (2H, m, $CH_3CH_2CH_2$-Ar), 4.12 (3H, s, $ArOCH_3$), 7.12 (1H, d, *J* 8.2, 7-H), 7.55 (1H, t, *J* 8.2, 6-H), 7.72 (1H, d, *J* 8.2, 5-H), and 9.02 (1H, s, 2-H); *m*/*z* (CI) 272 (MH^+, 100).

Further elution afforded **4-chloro-3-(1-hydroxybutyl)-8-methoxyquinoline** (**26)** (170 mg, 32%) as a white foam: δ_H (270 MHz) 0.91 [3H, t, *J* 7.7, $CH_3CH_2CH_2CH(OH)$], 1.30−1.59 [2H, m, $CH_3CH_2CH_2CH(OH)$], 1.67−1.87 [2H, m, $CH_3CH_2CH_2CH(OH)$], 3.02 (1H, br s, OH), 4.01 (3H, s, $ArOCH_3$), 5.26−5.32 [1H, m, $CH_3CH_2CH_2CH(OH)$], 7.00 (1H, d, *J* 8.2, 7-H), 7.47 (1H, t, *J* 8.2, 6-H), 7.67 (1H, d, *J* 8.2, 5-H), and 8.98 (1H, s, 2-H); *m*/*z* (EI) 265 (M^+, 89), 264 ($M^+ - H$, 100), 236 ($M^+ - C_2H_5$, 61), and 222 ($M^+ - C_3H_7$, 77).

***N,N*-Dimethyl 4-Chloro-8-methoxyquinoline-3-carboxamide (22b).** A suspension of dimethylamine hydrochloride (0.33 g, 4 mmol) in CH_2Cl_2 (10 cm^3) at 0−5 °C under N_2 was treated with a solution of pyridine (0.32 cm^3, 4 mmol) in CH_2Cl_2 (2 cm^3), added dropwise over 2 min, followed by a solution of 4-chloro-8-methoxy-3-quinolinecarbonyl chloride (**22a**) (1.0 g, 4 mmol) in CH_2Cl_2 (15 cm^3) added dropwise over 10 min. The resulting solution was stirred at 0−5 °C for 1 h, allowed to reach ambient temperature over 25 min, and stirred for a further 2 h. The resulting brown suspension was partitioned between EtOAc (25 cm^3) and saturated $NaHCO_3$ solution (15 cm^3) and the organic layer washed with brine (15 cm^3), dried, and evaporated to give a yellowish solid, which was crystallised from EtOAc/hexane to give the chloro carboxamide **22b** (0.73g, 69%) as white needles: mp 150−152 °C (Found: M^+ (EI), 264.0651; $C_{13}H_{13}ClN_2O_2$ requires *m*/*z* 264.0666); ν_{max} ($CHCl_3$)/cm^{-1} 1640 (C═O); δ_H (270 MHz) 2.87 (3H, s, NCH_3), 3.16 (3H, s, NCH_3), 4.05 (3H, s, $ArOCH_3$), 7.11 (1H, d, *J* 8.0, 7-H), 7.57 (1H, t, *J* 8.0, 6-H), 7.78 (1H, d, *J* 8.0, 5-H), and 8.73 (1H, s, 2-H); δ_C (62.5 MHz) 35.0 (NCH_3), 38.0 (NCH_3), 56.5 ($ArOCH_3$), 109.9, 116.0, 127.0, 128.8, 130.0, 138.7, and 141.0 (Ar C), 146.4 (2-C), 155.6 (8-C), and 166.4 (CO); *m*/*z* (FIA) 265 (MH^+, 100), 250 ($MH^+ - CH_3$, 18), 222 ($MH^+ - CONH$, 30), and 206 [$MH^+ - CH_3 - N(CH_3)_2$, 50].

Conversion of Chloro Carboxamide 22b to 1a. The chloro carboxamide **22b** (0.73 g, 2.8 mmol) was heated with 2-toluidine (0.3 cm^3, 2.8 mmol) in refluxing 1,4-dioxane (10 cm^3) for 2 h. The reaction mixture was partitioned between EtOAc (20 cm^3) and saturated $NaHCO_3$ solution (10 cm^3) and the organic layer dried and evaporated to give the crude product as a brown oil (1.2 g). The latter was chromatographed on silica gel (100 g) eluting with 9:1 EtOAc/MeOH to give initially starting chloro carboxamide **22b** (0.2 g, 27%) followed by ***N,N*-dimethyl 8-methoxy-4-[(2-methylphenyl)-amino]quinoline-3-carboxamide (23)** (0.45 g, 48%) as a yellow solid: δ_H (270 MHz) 2.40 (3H, s, $ArCH_3$), 3.08 [6H, br s, $N(CH_3)_2$], 4.08 (3H, s, $ArOCH_3$), 6.67−6.74 (1H, m, Ar), 6.97−7.07 (3H, m, Ar), 7.21−7.30 (3H, m, Ar), and 8.71 (1H, s, 2-H).

To a solution of the amino amide **23** (0.187 g, 0.56 mmol) in dry THF (5 cm^3) at ambient temperature under N_2 was added PrMgCl (0.56 cm^3 of a 2 M solution in THF, 1.12 mmol) dropwise over 1 min, and the stirring was continued at ambient temperature for 1 h and then at reflux for 1 h.

The cooled solution was poured into chilled HCl (1 M, 10 cm^3) solution, basified with NaOH solution (2 M, 7.5 cm^3), and extracted into EtOAc (10 cm^3). The organic layer was washed with brine (7.5 cm^3), dried, and evaporated to give the crude product as a viscous yellow oil (0.10 g), HPLC analysis of which showed the presence of **1a** (18%).

Ethyl 8-Methoxy-4-[(2-methylphenyl)amino]quinoline-3-carboxylate (20). One-Pot Procedure. A solution of diethyl (ethoxymethylene)malonate (**17**) (44.25 g, 205 mmol) and 2-anisidine (**16**) (22.56 cm^3, 200 mmol) in BuOAc (120 cm^3) was heated at reflux under N_2 for 1 h. Azeotropic distillation of EtOH was conducted until the head temperature had reached 124−126 °C. The distillate removed was replaced by an equal volume of BuOAc (∼35 cm^3) and the resulting orange solution of the [(arylamino)methylene]-malonate **18** allowed to cool to ambient temperature.

In a separate flask, a solution of $POCl_3$ (37.3 cm^3, 400 mmol) in BuOAc (120 cm^3) was heated to ∼70 °C under N_2. Freshly prepared PPSE[19] (2.79 g) was added with stirring and the resulting solution heated to reflux. The refluxing solution was treated with the solution of the [(arylamino)-methylene]malonate **18** prepared above, added dropwise over 7 h. The reaction mixture was allowed to cool to ∼80 °C, and 2-toluidine (42.85 g, 400 mmol) was added dropwise over 15 min, the temperature being kept below 100 °C. The resulting mixture was heated at reflux for 1 h. After being cooled to ∼70 °C, the reaction mixture was quenched by the cautious addition of aqueous NaOH (2 M, ∼500 cm^3), the temperature being kept at 70−80 °C such that the pH reached >7. The organic layer was washed with water (100 cm^3) at 70−80 °C. The organic solution was concentrated by distillation at atmospheric pressure to allow the collection of BuOAc (120 cm^3) together with a small quantity of water. The cooled residual solution was stirred at 0 °C for 2 h, and the resulting solid was collected via suction filtration, washed with chilled *i*-PrOH (100 cm^3), and dried under reduced pressure to give the quinoline ester **20**[12] as pale yellow crystals (47.6 g, 71%), mp 193−194 °C, identical to the product prepared previously.

Activation of Zinc.[22] Zinc powder was activated by sequential washing with (i) HCl (20%) solution, (ii) water (until the washings became neutral), (iii) acetone, and (iv) ether and dried for 1 h under a low vacuum.

3-Ethyl-7-methoxy-1-(2-methylphenyl)benzo[h]-1,6-naphthyridine-2,4(1*H*,3*H*)-dione (29). A refluxing suspension of activated zinc (1.17 g, 18 mmol) in THF (10 cm^3) under N_2 was treated with a solution of the quinoline ester **20** (1 g, 2.98 mmol) in THF (5 cm^3) added all at once followed by a solution of methyl 2-bromobutyrate (**27a**) (2.7 g, 14 .9 mmol) in THF (5 cm^3) added over 1 h. The reaction mixture was heated under reflux for a further 1 h and cooled and the THF removed *in vacuo* to leave a residue which was partitioned into CH_2Cl_2 (20 cm^3)/water (20 cm^3). The organic phase was washed with water (10 cm^3), dried, and evaporated to give the crude keto ester **28a** (1.16 g) as a brown oil. The keto ester **28a** (1.16 g, 2.96 mmol) and KOH (0.7 g, 12.5 mmol) were heated in a refluxing mixture of MeOH (10 cm^3) and water (10 cm^3) for 2 h. The solvents were removed *in vacuo*, and the residue was taken up in water (20 cm^3), acidified with HCl (1 M, 15 cm^3) solution, and extracted into CH_2Cl_2 (2 × 25 cm^3). The combined organic extracts were dried and evaporated to give a brown oil, which was chromatographed on silica gel with 9:1 $CHCl_3$/MeOH to give a pale oil, which was crystallised from EtOAc/MeOH to give the keto lactam **29** (0.80 g, 75%) as a pale yellow solid: mp 236−241 °C (Found: M^+ (EI) 360.1461. $C_{22}H_{20}N_2O_3$ requires *m*/*z* 360.1474); ν_{max} (Nujol mull)/cm^{-1} 1673 (C═O), 1606 (Ar), and 1559 (Ar); δ_H (400 MHz) 1.14 (3H, t, *J* 7.3, C*H*$_3$CH$_2$), 2.02 (3H, s, ArCH$_3$), 2.85 (2H, q, *J* 7.3, CH$_3$C*H*$_2$), 4.01 (3H, s, ArOCH$_3$), 6.42−6.50 (1H, m, Ar), 7.00−7.08 (2H, m, Ar), 7.17−7.22 (1H, m, Ar), 7.34−7.49 (3H, m, Ar), 9.81 (1H, s, 5-H), and 10.37 (1H, br s, OH); δ_C (100 MHz) 12.7 (*C*H$_3$CH$_2$), 17.6 (ArCH$_3$), 17.7 (CH$_3$*C*H$_2$), 56.2 (ArOCH$_3$), and 109.1−164.6 (18 C, Ar C); *m*/*z* (FIA) 361 (MH^+, 100) and 329 ($M^+ - OCH_3$, 28).

***tert*-Butyl 3-[8-Methoxy-4-[(2-methylphenyl)amino]-quinol-3-yl]-2-ethyl-3-oxopropanoate (28d).** A stirred suspension of activated zinc (10.6 g, 0.163 mol) in THF (50 cm^3) was treated with a warm (∼50 °C) solution of the quinoline ester **20** (10 g, 30 mmol) in THF (85 cm^3) added all at once followed by a solution of *tert*-butyl 2-bromobutyrate (**27d**)[21] (29.8 g, 0.134 mol) in THF (30 cm^3) added dropwise over 1 h. The reaction mixture was heated under reflux for a further 2 h. After cooling to ambient temperature, ∼60 cm^3 of THF was removed by distillation *in vacuo* and the residue poured into EtOAc (200 cm^3)/water (200 cm^3). The aqueous solution was extracted with more EtOAc (100 cm^3), and the combined organic solutions were stirred at ambient temperature for 1 h. The solids were removed by suction filtration through Celite and rinsed with EtOAc (2 × 100 cm^3). The combined organic solutions were washed with brine (100 cm^3), dried, and evaporated to give an orange oil (22 g). The latter was triturated with hexane (200 cm^3) to give a yellow solid, which was filtered off, washed with hexane, and dried in air to give the crude product (15 g), which required additional work-up to remove zinc compounds. The crude product was taken up in EtOAc (150 cm^3) and the solution washed with aqueous NaOH (6 M, 75 cm^3) solution and brine (75 cm^3), dried, and evaporated to give the keto ester **28d** (12 g, 92%) as an orange oil. Crystallisation from EtOAc/hexane afforded a yellow crystalline solid (8.25 g, 63%): mp 107−109 °C (Found: C, 71.78; H, 6.92; N, 6.42. $C_{26}H_{30}N_2O_4$ requires C, 71.87; H, 6.96; N, 6.45%); ν_{max} (KBr)/cm^{-1} 1728 (CO$_2$-*t*-Bu), 1723 (C═O), 1639 (Ar), 1589 (Ar), and 1522 (Ar); δ_H (400 MHz) 1.04 (3H, t, *J* 7.4, C*H*$_3$CH$_2$CH), 1.43 [9H, s, (CH$_3$)$_3$C], 2.02−2.17 (2H, m, CH$_3$C*H*$_2$CH), 2.34 (3H, s, ArCH$_3$), 4.05 (3H, s, ArOCH$_3$), 4.30 (1H, t, *J* 7.9, CH$_3$CH$_2$C*H*), 6.90−7.30 (7H, m, Ar), 9.25 (1H, s, 2-H), and 11.20 (1H, s, NH); δ_C (100 MHz) 12.1 (*C*H$_3$CH$_2$), 18.2 (ArCH$_3$), 22.9 (CH$_3$*C*H$_2$), 27.9 [(*C*H$_3$)$_3$C)], 56.0 (ArCH$_3$), 57.1 (CO*C*HCO$_2$-*t*-Bu), 82.0 [(CH$_3$)$_3$*C*], 110.0, 112.5, 118.1, 120.2, 124.1, 124.4, 125.8, 126.6, 131.0, 132.1, 140.6, 141.8, 150.4, 153.4, and 155.4 (15C, Ar C), 169.0 (*C*O$_2$-*t*-Bu), and 198.1 (CO); *m*/*z* (FIA) 435 (MH^+, 38), 379 ($MH^+ - C_4H_8$, 39), and 335 ($MH^+ - C_4H_8 - CO_2$, 100).

Conversion of Ester 20 to 1a. A stirred refluxing mixture of activated zinc (10.6 g, 0.163 mol) in THF (50 cm^3) under N_2 was treated with a solution of the quinoline ester **20** (10.0 g, 30 mmol) in THF (85 cm^3) added all at

once followed by a solution of *tert*-butyl 2-bromobutyrate (**27d**)[21] (30 g, 135 mmol) in THF (30 cm^3) added dropwise over 1 h. The reaction mixture was refluxed for a further 2 h and then stirred at ambient temperature for 18 h. Then ~60 cm^3 of THF was removed by distillation *in vacuo* and the residual mixture partitioned into EtOAc (200 cm^3)/water (200 cm^3). The aqueous solution was re-extracted with EtOAc (100 cm^3), and the combined organic phases were stirred at ambient temperature for 1 h. The solids were removed by filtration through Celite, and the bed was washed with fresh EtOAc (2 × 100 cm^3). The combined organic solutions were washed with NaOH solution (6 M, 3 × 100 cm^3) and brine (100 cm^3), dried, and concentrated *in vacuo* to give the crude keto ester **29d** as a yellow oil. The latter was heated in a refluxing mixture of formic acid (25 cm^3) and water (25 cm^3) for 1.5 h. The reaction mixture was cooled to <20 °C and treated dropwise with NaOH solution (6 M, ~130 cm^3) until the solution pH reached ~10. EtOAc (100 cm^3) was added and the resulting mixture warmed to 50 °C to effect solution. The organic layer was washed with brine (50 cm^3), filtered, and concentrated *in vacuo* to a volume of ~30 cm^3. The solution was cooled to 0−5 °C and the resulting precipitated solid filtered off, washed with 20% EtOAc in hexane (2 × 15 cm^3), and dried under reduced pressure to give **1a** (7.28 g, 73%) as yellow crystals, identical to the compound reported previously.[1]

3-Butyryl-8-hydroxy-4-[(2-methylphenyl)amino]quinoline (1c). Method A. Using HBr. A solution of 3-butyryl-8-methoxy-4-[(2-methylphenyl)amino]quinoline[1] (**1a**) (10.03 g, 30 mmol) in DMF (100 cm^3) was treated with HBr in AcOH (45%, 5.4 cm^3, 30 mmol) under N_2 and heated under reflux for 22 h. The cooled mixture was poured into saturated aqueous $NaHCO_3$ (500 cm^3) and extracted into EtOAc (2 × 100 cm^3). The organic extracts were combined, washed with water (4 × 75 cm^3) and brine (75 cm^3), dried, and evaporated to give the crude product as a yellow solid (10 g). Recrystallisation from *s*-BuOH (90 cm^3) afforded the 8-hydroxyquinoline[2] **1c** (6 g, 62.5%) as pale yellow crystals: mp 112−114 °C (lit.[2] mp 114−115 °C); ν_{max} (Nujol mull)/cm^{-1} 3050 (NH), 1640 (C═O), and 1595 (Ar); δ_H (400 MHz) 1.08 (3H, t, *J* 7.4, $CH_3CH_2CH_2CO$), 1.87 (2H, sextet, *J* 7.4, $CH_3CH_2CH_2CO$), 2.33 (3H, s, $ArCH_3$), 3.12 (2H, t, *J* 7.4, $CH_3CH_2CH_2CO$), 6.80−7.35 (7H, m, Ar), 9.10 (1H, s, 2-H), and 12.29 (2H, br s, OH, NH).

Method B. Using Lithium Iodide. A solution of the 8-methoxyquinoline **1a** (3.6 g, 10.8 mmol) in 2,4,6-collidine (7.2 cm^3, 54.7 mmol) was treated with anhydrous LiI (2.16 g, 16 mmol) and the mixture heated at 120 °C under N_2 for 19 h. The cooled reaction mixture was treated with HCl (2 M, 20 cm^3) and extracted into CH_2Cl_2 (20 cm^3). The organic extract was washed with HCl (2 M, 2 × 20 cm^3), saturated aqueous $NaHCO_3$ (20 cm^3), and water (20 cm^3), dried, and evaporated to give a yellow solid, which was recrystallised from *i*-PrOH (60 cm^3) to give the 8-hydroxyquinoline **1c** (2.87 g, 83%) as yellow crystals identical to the product previously reported.

Method C. Using Lithium Bromide/Lithium Iodide. The 8-methoxyquinoline **1a** (2.0 g, 6 mmol) was taken up in 2,4,6-collidine (4 cm^3, 30.4 mmol) and the solution treated with a mixture of anhydrous LiBr (0.79 g, 9 mmol) and $LiI{\cdot}xH_2O$ (0.17 g, 0.9 mmol). The mixture was heated at 140 °C for 5 h. HPLC analysis of the solution revealed the presence of the desired 8-hydroxyquinoline **1c** (96%) and starting material **1a** (3%).

4-Hydroxy-11-methyl-7-propyldibenzo[*b*,*h*][1,6]-naphthyridine (30). The 8-hydroxyquinoline **1c** (15 g, 47 mmol) was taken up in concd HCl (specific gravity 1.18, 250 cm^3) and the solution heated under reflux for 1 h. After cooling to ambient temperature, solid $NaHCO_3$ (200 g) was cautiously added portionwise with rapid stirring and with external cooling. The resulting solid was filtered off, washed with water (3 × 50 cm^3), and dried under reduced pressure over P_2O_5. The crude product was recrystallised from *i*-PrOH to give the tetracyclic compound **30** (12.6 g, 83%) as yellow needles: mp 177 °C (Found: M^+ (EI) 302.1433. $C_{20}H_{18}N_2O$ requires 302.1419); ν_{max} (Nujol mull)/cm^{-1} 3304 (OH), 1614 (Ar), and 1559 (Ar); δ_H (400 MHz) 1.11 (3H, t, *J* 7.5, $CH_3CH_2CH_2CO$), 1.86 (2H, sextet, *J* 7.5, $CH_3CH_2CH_2CO$), 2.98 (3H, s, $ArCH_3$), 3.55 (2H, t, *J* 7.5, $CH_3CH_2CH_2CO$), 7.30−7.35 (1H, m, Ar), 7.45−7.50 (1H, m, Ar), 7.58−7.70 (2H, m, Ar), 8.02−8.07 (1H, m, Ar), 8.70−8.75 (1H, m, Ar), and 9.42 (1H, s, 6-H); δ_C (100 MHz) 14.4 ($CH_3CH_2CH_2$), 18.5 ($CH_3CH_2CH_2$), 25.4 ($ArCH_3$), 28.8 ($CH_3CH_2CH_2$), 113.1, 115.1, 117.4, 122.3, 125.5, 126.1, 126.4, 128.5, 131.0, 133.9, 138.5, 146.0, 148.5, 148.9, 149.5, and 152.5 (16C, Ar C); *m*/*z* (FIA) 303 (MH^+, 100) and 274 ($MH^+ - NH{=}CH_2$, 70).

3-Butyryl-8-(2-hydroxyethoxy)-4-[(2-methylphenyl)-amino]quinoline (1b). Method A. Molten ethylene carbonate (2.6 kg, 29.5 mol) was heated to 90 °C and treated with the 8-hydroxyquinoline **1c** (260 g, 0.81 mol), added portionwise over ~5 min. The mixture was reheated to 90 °C and the resulting suspension treated with anhydrous K_2CO_3 (11.2 g, 81 mmol). The reaction mixture was heated at 90 °C for 3.5 h and subsequently allowed to cool to ~60 °C before water (2 dm^3) was added with stirring. The resulting slurry was poured into more water (2 dm^3) and stirring continued for 45 min. The solid was collected via suction filtration, washed with water, and dried at 50 °C to give a crude product (277 g), which was recrystallised from EtOAc (5 dm^3) to give **1b**[2] (233 g, 71%) as yellow crystals: mp 115−118 °C (lit.[2] mp 117−120 °C).

The mother liquors from the above were concentrated *in vacuo*, and the residue was triturated with toluene (60 cm^3). The resulting solid was filtered off, washed with toluene, and dried at 50 °C to give yellow crystals (12.7 g). A sample (1.22 g) of the latter was subjected to chromatography on silica gel, eluting with EtOAc to give **6-butyryl-7-[(2-methylphenyl)imino]-2,3-dihydro-7H-pyrido[1,2,3-*de*]-1,4-benzoxazine (31)** (0.6 g) as bright yellow crystals: mp 178−180 °C (Found: C, 76.2; H, 6.5; N, 7.9. $C_{22}H_{22}N_2O_2$ requires C, 76.3; H, 6.4; N, 8.1); ν_{max} (KBr)/cm^{-1} 1686 (C═O), 1670 (C═N), 1620 (C═C), 1605 (Ar), and 1560 (Ar); δ_H (270 MHz; [$^2H_6$]DMSO) 0.70 (3H, t, *J* 7.3, $CH_3CH_2CH_2CO$), 1.20 (2H, sextet, *J* 7.3, $CH_3CH_2CH_2CO$), 2.13 (3H, s, $ArCH_3$), 2.33 (2H, t, *J* 7.3, $CH_3CH_2CH_2CO$), 4.15−4.19 (2H, m, $-NCH_2CH_2O-$), 4.37-4.41 (2H, m, $-NCH_2CH_2O-$), 6.44−6.47 (1H, m, Ar), 6.75−6.81 (1H, m, Ar), 6.91−7.13 (4H, m, Ar), 7.65−7.67 (1H, m, Ar), and 7.71 (1H, s, 5-H); δ_C (62.5 MHz; [$^2H_6$]DMSO) 13.0 ($CH_3CH_2CH_2CO$), 16.7

($CH_3CH_2CH_2CO$), 17.4 ($ArCH_3$), 42.0 ($CH_3CH_2CH_2CO$), 47.5 ($-NCH_2CH_2O-$), 63.2 ($-NCH_2CH_2O-$), 115.9−150.9 (13C, Ar C and 7-C), 141.1 (5-C), and 199.1 (CO); *m*/*z* (EI) 346 (M^+, 30), 317 ($M^+ - C_2H_5$, 100), 303 ($M^+ - C_3H_7$, 13), and 275 ($M^+ - C_3H_7CO$, 53).

Crude **1b** prepared as above (70 g) was chromatographed on silica gel (200 g) eluting with acetone followed by 5% MeOH in acetone to give the crude carbonate **32** (0.5 g) as the earlier eluting fraction, the bulk (0.3 g) of which was rechromatographed on silica gel (50 g) eluting with CH_2Cl_2 to give **bis[[[3-butyryl-4-[(2-methylphenyl)amino]quinol-8-yl]oxy]ethyl] carbonate** (**32**) (0.28 g) as a yellow foam: δ_H (400 MHz) 1.02 (3H, t, *J* 7.4, $CH_3CH_2CH_2CO$), 1.80 (2H, sextet, *J* 7.4, $CH_3CH_2CH_2CO$), 2.34 (3H, s, $ArCH_3$), 3.07 (2H, t, *J* 7.4, $CH_3CH_2CH_2CO$), 4.42−4.49 (2H, m, $ArOCH_2CH_2OCO$), 4.70−4.75 (2H, m, $ArOCH_2CH_2OCO$), 6.85−7.30 (7H, m, Ar), 9.25 (1H, s, 2-H), and 11.80 (1H, s, NH); δ_C (100 MHz) 13.9 ($CH_3CH_2CH_2CO$), 18.2 ($CH_3CH_2CH_2CO$), 18.5 ($ArCH_3$), 41.7 ($CH_3CH_2CH_2CO$), 65.9 ($ArOCH_2CH_2OCO$), 66.5 ($ArOCH_2CH_2OCO$), 111.7−155.0 (16C, Ar C, OCO.O), and 203.1 (ArCO); *m*/*z* (FAB) 755 (MH^+, 8) and 347 [M(**32**)H^+, 100].

Method B. The 8-hydroxyquinoline **1c** (10 g, 31.2 mmol) was stirred with *i*-PrOH (60 cm^3) to give a thick slurry. Ethylene carbonate (13.21 g, 0.15 mol) was added and the mixture heated to give a clear solution. Following addition of DABCO (0.5 g, 4.5 mmol) the mixture was heated at reflux for 10 h. HPLC analysis of the reaction solution revealed mainly desired product **1b** together with small quantities of the tricyclic compound **31**, the symmetrical carbonate **32** (both identified by HPLC comparison with samples isolated above), and **[[3-butyryl-4-[(2-methylphenyl)amino]quinol-8-yl]oxy]ethyl 2-methylethyl carbonate** (**33**), assigned on the basis of LC-ionspray-MS, *m*/*z* 451 (MH^+, 100), 409 ($MH^+ - C_3H_6$, 26), 365 ($MH^+ - C_3H_6 - CO_2$, 44), and 321 ($MH^+ - C_3H_6 - CO_2 - C_2H_4O$, 36).

Water (40 cm^3) was added to the reaction mixture, and the product crystallised on cooling. The suspension was stirred for 18 h at ambient temperature and the product collected via suction filtration, washed with 40% aqueous *i*-PrOH (20 cm^3), and air-dried to give the 8-(2-hydroxyethoxy)quinoline **1b** (7.7 g, 66%) as a yellow solid, mp 116−118 °C, identical to the product previously reported[2] and containing very low levels of impurities.

Method C. Ethylene carbonate (66.1 g, 0.75 mol) was taken up in *t*-BuOH (200 cm^3) at 40−50 °C, and the resulting solution was treated with the 8-hydroxyquinoline **1c** (50 g, 0.156 mol) and DABCO (2.5 g, 22.3 mmol). The solution was heated under reflux for 2 h. More *t*-BuOH (100 cm^3) and water (200 cm^3) were added with the temperature of the flask being maintained at >70 °C. The reaction mixture was subsequently cooled with rapid stirring to ∼10 °C. The resulting precipitated product was collected via suction filtration, washed with a chilled *i*-PrOH (120 cm^3)/water (80 cm^3) mixture, and dried under reduced pressure to give **1b**[2] (51.2 g, 90%) as a yellow crystalline solid: mp 118−120 °C; δ_H (400 MHz) 1.02 (3H, t, *J* 7.4, $CH_3CH_2CH_2CO$), 1.79 (2H, sextet, *J* 7.4, $CH_3CH_2CH_2CO$), 2.34 (3H, s, $ArCH_3$), 3.05 (2H, t, *J* 7.4, $CH_3CH_2CH_2CO$), 3.70 (1H, br s, OH), 4.04−4.07 (2H, m, $ArOCH_2CH_2OH$), 4.23−4.27 (2H, m, $ArOCH_2CH_2OH$), 6.90−7.30 (7H, m, Ar), 9.10 (1H, s, 2-H), and 11.97 (1H, s, NH).

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