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# SYNTHESIS OF PYRIDO[2,3-*b*]ACRIDINE-5,11,12-TRIONES

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***Abstract***: *N*-Protected 4-quinolones **5** were examined as starting materials for the synthesis of pyrido[2,3-*b*]acridine-5,11,12-triones **18**. Addition of the anion of pyridine *N*-oxide **7b** to **5** gave the pyrido[2,3-*b*]acridine-2,11-diones **9**. 2-Lithiation of **5a, b** and addition to aldehyde-ester **11b** gave a mixture of **15** and **16**, oxidation of either of which gave **18**. Copyright © 1996 Elsevier Science Ltd

Many heterocyclic natural products derived from marine organisms[1] have striking biological activities. This rôle as pharmaceutical lead compounds, taken with their limited availability from the natural sources, makes them prime candidates for total synthesis. We are examining approaches to several structural types of marine alkaloid, including substances in which one can discern a tetracyclic pyrido[2,3,4-*kl*]acridine unit:[2] those which concern us here can be represented by partial structure **1** in which an additional heterocyclic ring is fused to the tetracyclic nucleus. More than 35 such substances are known; examples include dercitine[3] and related substances,[4] kuanoniamine A, **2** and related substances,[5] which have a fused thiazole, shermilamine A[6] **3** and related products,[7,8] with a linked 2,3-dihydro-3-oxo-1,4-thiazine ring, and ascididemine[9] **4** and related compounds[10] with a fused pyridine.

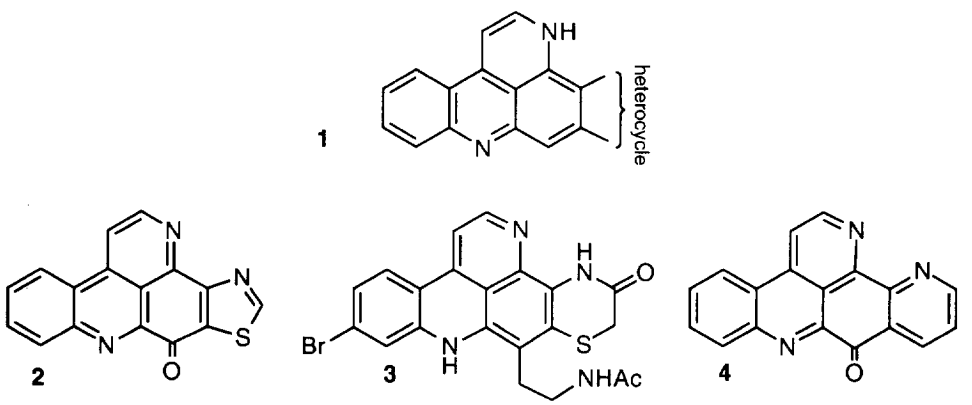
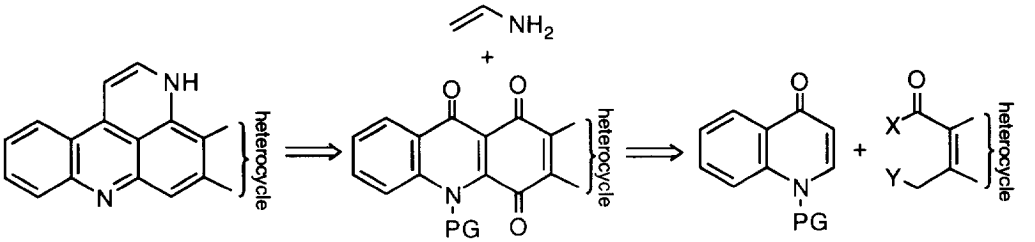



**Figure 1**

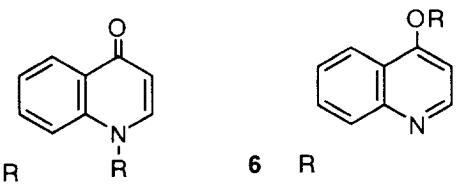
Our plans for the construction of such molecules, summarised in Scheme 1 and intended to be applicable to each structural variation, are based on previous explorations of 4-quinolone chemistry[11] and the use of

components to provide the 'right-hand' portion of the molecules which would be analogous to each other differing only in the particular heterocyclic ring, as appropriate. Substituents X and Y would be chosen to allow regioselective attachment to the 4-quinolone. We describe here a route to tetracyclic quinones of the type shown in Scheme 1, where the heterocyclic ring is a pyridine and thus the sequence is targeted at the ascididemine-type structures. The total syntheses of 2-bromoleptoclidinine,[12] ascididemine,[13] and kuanoniamines[14] using strategies different to that discussed here, have already been described.




**Scheme 1**

We have previously examined two ways in which 4-quinolones can be elaborated: by nucleophilic addition at C-2,[11b,c] and by 2-lithiation then reaction with an electrophile.[11a,c] In each case, subsequent electrophilic attack at C-3, in an intramolecular sense, can provide access to annelated quinolones. Our present studies utilised the 1-methyl- **5a**,[11a] 1-methoxycarbonyl- **5b**,[11d] 1-methoxyethoxymethyl- (MEM) **5c**, 1-(4-methylphenylsulfonyl)- (Ts) **5d**, and 1-trimethylsilylethoxymethyl- (SEM) **5e**, -4-quinolones. The last three were prepared by reaction of 4-quinolone with the appropriate electrophile using sodium hydride as base; in the last two cases the desired *N*-substituted derivatives were accompanied by minor amounts of the *O*-substituted 4-quinolinols **6a** and **6b**. The 2-lithiation of both SEM- and MEM-protected 4-quinolones, measured by quenching with $CD_3OD$, proceeded to the extent of >90% and is thus much more efficient than that of 1-methyl-4-quinolone, because the dimerisation which plagues the latter[11a] was totally absent for these two derivatives. In studying **5a** we had found that the use of 3 mol equivalents of LDA suppresses the tendency for dimer formation and so, in this work, we continued with this practice. The *N*-MEM-protected quinolone is to be preferred, because in its synthesis it is formed to the exclusion of *O*-derivative.

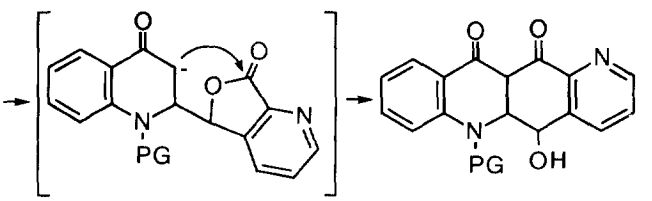



| **5** | R |
|---|---|
| **a** | Me |
| **b** | $CO_2Me$ |
| **c** | MEM |
| **d** | Ts |
| **e** | SEM |

| **6** | R |
|---|---|
| **a** | Ts |
| **b** | SEM |

**Figure 2**

It was hoped that the anion of the azaphthalide **7a**[15] would react with an *N*-substituted 4-quinolone by addition at C-2, then subsequent cyclisation by intramolecular attack by C-3 on the lactone carbonyl group (Scheme 2).[16] We examined each of **5a-e**, but addition took place only when the *N*-substituent was methoxycarbonyl. Even here, the desired subsequent cyclisation did not occur, and only **8** was isolated in small yield. This compound presented a $^1$H NMR spectrum with an ABX system for the C2-H-C3-$H_2$ unit of the tetrahydroquinolone ring. Proton decoupling and COSY (H-C) experiments allowed us to complete assignment of the $^1$H and $^{13}$C NMR spectra. Thus, H-$3_{ax}$ is the most deshielded (δ 3.26) of the C3 protons with a $J_{3ax\text{-}3eq}$ = 18.0 Hz and $J_{3ax\text{-}2ax}$ = 7.0 Hz; H-$3_{eq}$ (δ 3.05) has $J_{3eq\text{-}2ax}$ = 1.5 Hz. These coupling constants agree with predictions from the Karplus equation using dihedral angles (ϕ $H_{2ax}$-$H_{3ax}$ = 170° and ϕ $H_{2ax}$-$H_{3eq}$ = 40°) measured from a Dreiding® model with the azaphthalide unit equatorially oriented.




**Scheme 2**

Arguing that the electrophilic character of the lactone carbonyl group would be increased by *N*-oxidation, and that this might encourage the second stage of the desired sequence, we converted **7a** into its *N*-oxide **7b**. The interaction of this with sodium hydride and the 4-quinolones **5b-d** produced tetracyclic materials in small yields to which we assign structures **9a-c**, with the methoxycarbonyl *N*-protecting group having been lost in the first of these products. The structural assignments rest on a combination of appropriate molecular formulae and $^1$H NMR signals for 6 ring C-Hs, including pairs of related, *ortho*-coupled doublets at δ 6.72/8.25, 6.10/7.78, and 6.56/8.18 for **9a-c** respectively, for the pyridone ring protons.

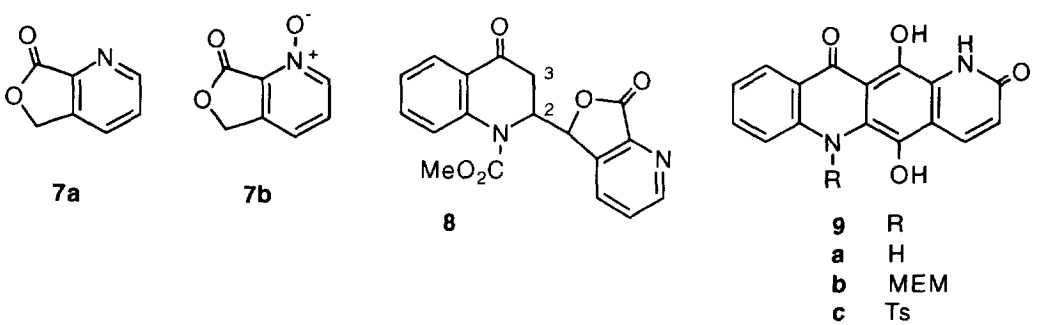
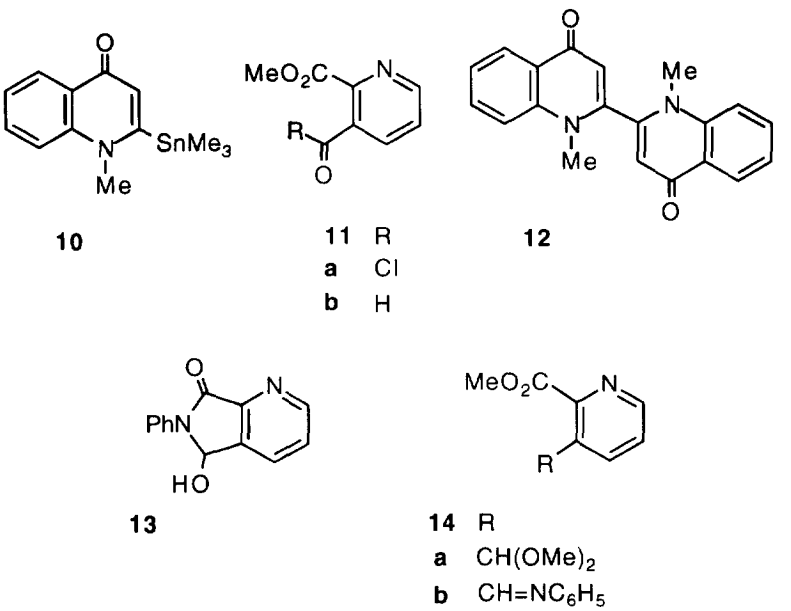



**Figure 3**

Turning to the alternative of using a 2-metallated 4-quinolone, we prepared 1-methyl-2-trimethylstannyl-4-quinolone **10** from the 2-lithiated species.[11a] Unfortunately, using a variety of conditions and catalysts, we

were unable to bring about coupling between the tin compound and the ester-acid chloride **11a**, with only dimer **12**[11a] being isolated. We turned instead to the corresponding aldehyde **11b** with the possibility of condensing it with 2-lithio-4-quinolones we expected that a second cyclisation step would then be required for formation of the target tetracycles. The aldehyde was prepared by an improvement of a patented route,[17] which involves 3-lithiation of *N*-phenylpicolinamide followed by formylation with DMF to give **13**. Methanolysis according to the published procedure gave imine **14b**. Much longer reaction times were required in order to form the pyridine ester-acetal **14a**, which was subsequentially deprotected to **11b** using improved trans-acetalisation conditions.




**10**

**11** R
**a** Cl
**b** H

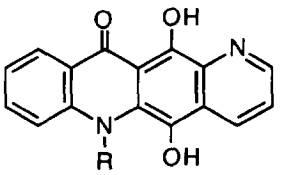
**12**

**13**

**14** R
**a** $CH(OMe)_2$
**b** $CH{=}NC_6H_5$

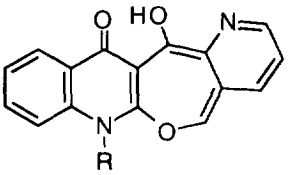
**Figure 4**

The reaction of lithiated 4-quinolones **5a** and **5c** (see above) with the pyridine aldehyde led, in each case, to a mixture of two isomeric, spectroscopically comparable substances, which could be separated by chromatography. The structures of one component of each pair of compounds were relatively straightforwardly determined. These products had only seven ring protons, three typical of a 2,3-disubstituted pyridine, and the remaining four of the disubstituted benzene – clearly, the heterocyclic ring of the original quinolone was now disubstituted and the linking atoms had to be the two substituent carbons of the pyridine reactant: structures **15a** and **15b**, or ones in which the pyridine ring is inverted are assigned. The regiochemistry shown in **15** was confirmed by an alternative synthesis starting from 2-formyl-1-methyl-4-quinolone[18] which on reaction with 3-lithiated *N,N*-diethylpicolinamide gave alcohol **17a**. This, on reaction with phosphoryl chloride, produced tetracyclic material identical with pyridoacridine **15a**. The formation of tetracyclic products directly from the lithiated quinolones was of course an unexpected bonus and is rationalized below.

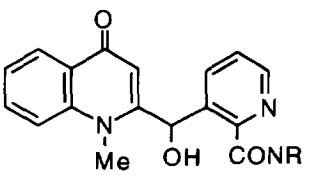


**15**

| | R |
|---|---|
| **a** | Me |
| **b** | MEM |



**16**



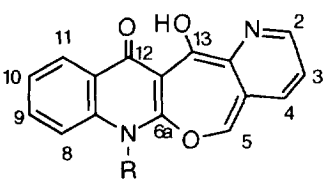
**17**

| | R |
|---|---|
| **a** | Et, Et |
| **b** | H, $C_6H_5$ |

**Figure 5**

The determination of structure of the isomeric products **16** was less simple and required, for our satisfaction, considerable study by NMR. Eight CH signals were present in the $^1H$ spectrum and confirmed by the $^{13}C$ NMR spectrum. Seven of these were easily assigned by proton decoupling , COSY (H-H and H-C) and HMBC experiments to the three pyridine and four benzene ring protons. However, the remaining CH signal, singlets at δ 8.60 and 8.61 for **16a** and **16b** respectively, needed further attention. For **16b** there was a positive NOE between the CH at δ 8.61 and the C4-H signal of the pyridine ring at δ 8.34 ppm, but we did not observe a NOE between the δ 8.61 proton and the N-$CH_2$ group. Exactly comparable results were obtained for **16a**: there was an NOE between the singlet at 8.60 and the pyridine proton at 8.35, but there was no NOE to the *N*-methyl. These experiments suggested that the unassigned CH is attached to C5 of the pyridine ring but is *not* linked to the quinolone ring. The correlations in the HMBC experiment are shown in Table 1. Finally, the correlation between C5-H (δ 8.61) and C6a (δ 179.5 ) and the low chemical shift for both signals corroborates the structures **16** proposed. The experiments discussed above allowed us to complete a detailed assignment of the NMR signals for **15** and **16** (Tables 2 and 3).

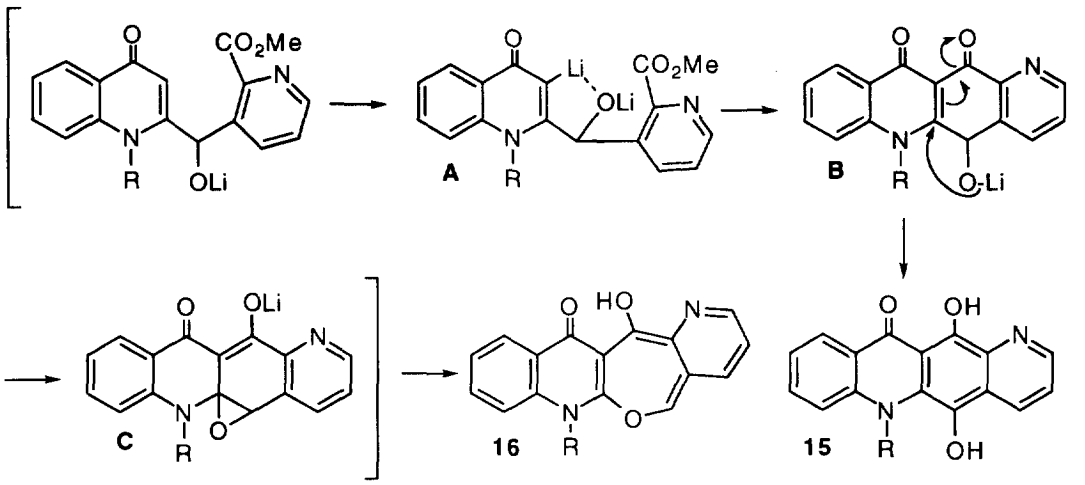
**Table 1. Long distance correlation (HMBC) for the compounds 16**



**16**

| | | | |
|---|---|---|---|
| H2→ C4 | H4→ C13a | H8→ C10 | H11→ C7a |
| H2→ C13a | H5→ C4 | H9→ C7a | H11→ C9 |
| H3→ C4a | H5→ C6a | H9→ C11 | H11→ C12 |
| H4→ C13 | H5→ C13 | H10→ C8 | H11→ C12a |
| H4→ C5 | H5→ C13a | H10→ C11a | |

In order to explain the formation of products **15** and **16** we propose the sequence summarised in Scheme 3. Thus, addition of the 2-lithioquinolone to the pyridine aldehyde would be followed by assisted lithiation[19] at the quinolone 3-position (→ **A**), then intramolecular acylation at C-3 (→ **B**) from which the tetracycles **15** are obtained by protonation during work up and tautomerisation. We envisage the formation of the isomers **16** as resulting from formation of epoxides **C** (arrows on **B**)[11b,c] followed by electrocyclic ring opening.




**Scheme 3**

Oxidation of **15b** with ceric ammonium nitrate (CAN) produced the corresponding quinone **18b** together with the *N*-deprotected quinone **18c** after a short reaction time, and exclusively **18c** in high yield after 15 minutes. Significantly, from the synthetic viewpoint, comparable treatment of the oxepines **16a** and **16b** also efficiently produced quinones **18a** and **18c** respectively. It is thus unnecessary to separate the isomers **15** and **16** before conversion into the tetracyclic quinones **18** required for further synthetic elaboration.

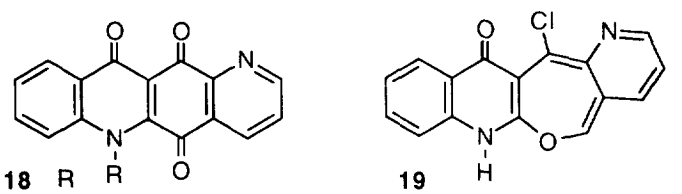


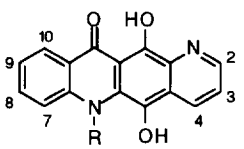
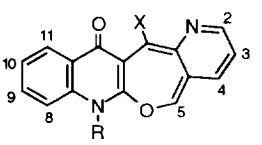
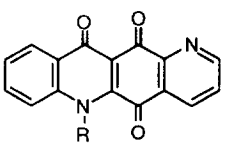

**Figure 6**

In the course of attempts to cyclise **17b** we treated it with thionyl chloride: it was converted into the chloro-oxepine, **19**

## Experimental Section

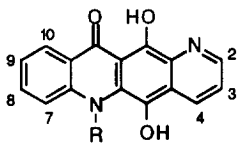
Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on $SiO_2$ (silica Gel 60 $F_{254}$, Merck 0.063-0.200 mm). The spots were located with iodoplatinate reagent or UV light. Column chromatography was carried out on $SiO_2$ (silica Gel 60 SDS 0.060-0.2 mm). Flash chromatography was carried out on $SiO_2$ (silica Gel 60 A CC (Merck). Drying of organic extracts during the work up of reactions was performed over anhydrous $Na_2SO_4$, and solutions were evaporated under reduced pressure with a rotatory evaporator. IR spectra were performed on a Nicolet 205 FT-IR and peaks are given in $cm^{-1}$. UV spectra were performed on a Hitachi U-2000 spectrophotometer. NMR spectra were performed on a Varian Gemini-200 (200 MHz), Varian Gemini-300 (300 MHz) and Varian VXR-500 (500 MHz); data are given in δ referred to TMS. MS spectra were performed on a Hewlett-Packard model 5989A; ions are recorded as *m/z* with percentage abundances relative to the molecular ion given in parentheses. Elemental analyses were performed on a Carlo Erba Fisons EA-1108 in the Serveis Científico-Tècnics de la Universitat de Barcelona.

**Table 2. $^1$H NMR Data for 15, 16, 18 and 19**

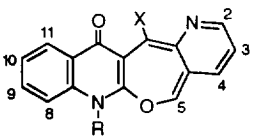
| |  **15** | |  **16** (X= OH) and **19** (X= Cl) | | |  **18** | | |
|---|---|---|---|---|---|---|---|---|
| $^1$H-NMR | **15a**[a] (R= Me) | **15b**[a] (R= MEM) | **16a**[a] (R= Me) | **16b**[a] (R= MEM) | **19**[a] (R= H) | **18a**[a] (R= Me) | **18b**[a] (R= MEM) | **18c**[b] (R= H) |
| OMe | – | 3.35 | – | 3.35 | – | – | 3.20 | – |
| $CH_2O$ | – | 3.56 | – | 3.56 | – | – | 3.52 | – |
| $CH_2O$ | – | 3.81 | – | 3.81 | – | – | 3.80 | – |
| $NCH_2$ | – | 6.10 | – | 6.11 | – | – | 6.00 | – |
| NMe | 4.22 | – | 4.23 | – | – | 4.13 | – | – |
| H2 | 8.89 | 8.87 | 8.85 | 8.86 | 8.93 | 9.00 | 9.04 | 9.01 |
| H3 | 7.34 | 7.36 | 7.39 | 7.41 | 7.68 | 7.73 | 7.77 | 7.91 |
| H4 | 8.75 | 8.73 | 8.35 | 8.34 | 8.70 | 8.55 | 8.58 | 8.48 |
| H5 | – | – | 8.60 | 8.61 | 8.09 | – | – | – |
| H7 | 7.45 | 7.76 | – | – | – | 7.71 | 7.94 | 8.14 |
| H8 | 7.21 | 7.70 | 7.50 | 7.82 | 7.08 | 7.80 | 8.57 | 7.79 |
| H9 | 7.24 | 7.25 | 7.30 | 7.70 | 7.65 | 7.51 | 7.51 | 7.49 |
| H10 | 8.38 | 8.34 | 7.24 | 7.26 | 7.75 | 8.51 | 8.47 | 8.20 |
| H11 | – | – | 8.45 | 8.41 | 8.20 | – | – | – |

a: Recorded in $CDCl_3$ solution; b: Recorded in DMSO-$d_6$ solution

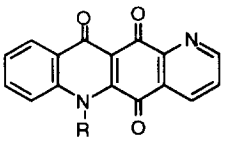
**Table 3. $^{13}C$ NMR Data for 15, 16, 18 and 19**



**15**



**16** (X= OH) and **19** (X= Cl)



**18**

| $^{13}C$-NMR | **15a**[a] (R= Me) | **15b**[a] (R= MEM) | **16a**[a] (R= Me) | **16b**[a] (R= MEM) | **19**[a] (R= H) | **18a**[a] (R= Me) | **18b**[a] (R= MEM) | **18c**[b] (R= H) |
|---|---|---|---|---|---|---|---|---|
| OMe | – | 59.0 | – | 58.9 | – | – | 58.9 | – |
| $CH_2O$ | – | 67.0 | – | 66.9 | – | – | 68.4 | – |
| $CH_2O$ | – | 71.8 | – | 71.7<br>79.9 | – | – | 72.1 | – |
| $NCH_2$ | – | 80.0 | – | | – | – | 79.7 | – |
| NMe | 56.3 | – | 39.8 | – | – | 40.2 | – | – |
| C2 | 153.8 | 152.0 | 179.4 | 150.4 | 154.3 | 152.3 | 154.3 | 153.4 |
| C3 | 120.6 | 118.6 | 120.6 | 120.7 | 128.0 | 126.3 | 126.3 | 129.1 |
| C4 | 134.6 | 133.2 | 138.2 | 137.7 | 135.0 | 134.2 | 133.9 | 134.6 |
| C5 | – | – | 117.0 | 117.2 | 124.2 | 182.9 | – | 179.4 |
| C5a | – | 129.5 | | | | 148.8 | 142.50 | 144.5 |
| C6a | – | 140.0 | 179.4 | 179.5 | | 141.8 | 135.37 | 138.0 |
| C7 | 116.4 | 116.5 | – | – | – | 117.5 | 118.9 | 120.6 |
| C7a | – | – | 146.3 | 145.2 | | – | | – |
| C8 | 135.0 | 135.3 | 115.4 | 116.8 | 118.0 | 135.7 | 135.0 | 133.4 |
| C9 | 122.12 | 121.7 | 134.7 | 134.6 | 131.2 | 127.7 | 127.2 | 125.8 |
| C10 | 127.7 | 126.3 | 120.8 | 121.8 | 129.0 | 128.9 | 128.8 | 125.7 |
| C10a | – | 114.0 | – | | | 129.9 | 134.39 | 130.7 |
| C11 | – | 184.7 | 127.6 | 127.0 | 130.0 | 178.9 | – | 174.8 |
| C11a | – | 120.2 | 122.6 | 122.6 | – | 140.5 | | 130.7 |
| C12 | – | 155.1 | 179.4 | 179.5 | – | 179.6 | 182.16 | 179.1 |
| C12a | – | 125.1 | 117.0 | 118.1 | – | 148.5 | – | 146.7 |
| C13 | – | – | 138.5 | 138.5 | – | – | – | – |
| C13a | – | – | 140.1 | 139.6 | – | – | – | – |

a: Recorded in $CDCl_3$ solution; b: Recorded in DMSO-$d_6$ solution

**1-(2-Methoxyethoxymethyl)-4-quinolone (5c).** To a suspension of oil-free NaH (550 mg, 13.8 mmol) in dry THF (20 ml) cooled at -78 °C, 4-quinolone (1.0 g, 6.9 mmol) was added under $N_2$. The mixture was

stirred for 30 min at -78 °C and 30 min at rt. The reaction mixture was cooled again to -78 °C and MEMCl (1.2 ml, 10.6 mmol) was added by syringe and the stirring continued for 30 min at -78 °C and 3 h at rt. After this time $H_2O$ was added, the organic solvent was evaporated and the residue was dissolved in $CH_2Cl_2$, washed with $H_2O$, dried and evaporated. The residue was purified by column chromatography. Elution with $CH_2Cl_2$-MeOH (98:2) gave quinolone **5c** (1.2 g, 75%) as a solid mp 71-72 °C ($CH_2Cl_2$): IR (KBr) 1650, 1625, 1600, 1495. $^1$H-NMR (300 MHz, $CDCl_3$) δ 3.36 (s, 3H); 3.45-3.75 (m, 4H); 5.54 (s, 2H); 6.22 (d, *J* = 7.8 Hz, 1H); 7.27-7.34 (m, 1H); 7.66 (d, *J* = 7.8 Hz, 1H); 7.66 (m, 2H); 8.4 (d, *J* = 7.6 Hz, 1H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 59.6 (q); 68.0 (t); 72.4 (t); 83.5 (t); 110.3 (d); 116.8 (d); 124.7 (d); 127.2 (d); 127.4 (s); 132.8 (d); 140.2 (s); 143.3 (d); 179.2 (s). MS (EI) 233 ($M^+$, 25), 158 (53), 89 (100). HRMS calcd for $C_{13}H_{15}NO_3$ 233.2655, found 233.6653.

**1-(*p*-Toluensulfonyl)-4-quinolone (5d) and 4-quinolyl *p*-toluenesulfonate (6a).** To a suspension of oil-free NaH (827 mg, 41.4 mmol) in dry THF (60 ml) cooled at -78 °C, 4-quinolone (3.0 g, 20.7 mmol) was added under $N_2$. The mixture was stirred for 30 min at -78 °C then a solution of TsCl (3.94 g, 20.7 mmol) in dry THF (10 ml) was added. The resulting mixture was stirred during 1 h at -78 °C and 3 h at rt. After this time $H_2O$ was added, the organic solvent was evaporated and the residue was dissolved in $CH_2Cl_2$ and washed with $H_2O$. The organic solution was dried and evaporated. The residue was crystallised from $C_6H_{14}$-$Et_2O$ to obtain the *N*-sulfonylated quinolone **5d** (2.2 g, 40%) as a solid mp 126-127 °C ($Et_2O$): IR (KBr) 1650, 1610, 1470. $^1$H-NMR (200 MHz, $CDCl_3$) δ 2.19 (s, 3H); 6.27 (d, *J* = 8.6 Hz, 1H); 7.16 (d, *J* = 8.7 Hz, 2H); 7.21 (ddd, *J* = 8.6, 8.0 and 1.0 Hz, 1H); 7.46 (ddd, *J* = 8.6, 8.0 and 1.8 Hz, 1H); 7.75 (d, *J* = 8.7 Hz, 2H); 8.07 (dd, *J* = 8.6 and 1.0 Hz, 1H); 8.18 (dd, *J* = 8.0 and 1.8 Hz, 1H); 8.46 (d, *J* = 8.6 Hz, 1H). $^{13}$C-NMR (75.4 MHz, $CDCl_3$) δ 22.2 (q); 113.0 (d); 118.7 (d); 126.2 (d); 127.6 (d); 127.0 (s); 128.0 (d); 130.9 (d); 133.3 (d); 134.3 (s); 137.0 (s); 138.4 (d); 146.9 (s); 179.0 (s). HRMS calcd for $C_{16}H_{13}NO_3S$ 299.3427, found 299.3431. Evaporation of the filtrate gave the *O*-sulfonylated quinoline **6a** as an oil (2.1 g, 38%): IR (Film) 1585, 1501, 1414, 1233. $^1$H-NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3H); 7.23 (d, *J* = 8.5 Hz, 2H); 7.55 (d, *J* = 6.0 Hz, 1H); 7.59 (ddd, *J* = 8.5, 8.5 and 1.0 Hz, 1H); 7.81 (ddd, *J* = 8.5, 7.7 and 1.4 Hz, 1H); 7.88 (d, *J* = 8.5 Hz, 2H); 8.07 (dd, *J* = 8.5 and 1.4 Hz, 1H); 8.24 (dd, *J* = 7.7 and 1.0 Hz, 1H); 8.55 (d, *J* = 6.0 Hz, 1H). $^{13}$C-NMR (70.4 MHz, $CDCl_3$) δ 21.3 (q); 105.8 (d); 120.0 (d); 120.4 (s); 123.9 (d); 125.8 (d); 127.6 (d); 129.1 (d); 134.4 (d); 139.3 (s); 141.0 (s); 143.8 (d); 170.5 (d). HRMS calcd for $C_{16}H_{13}NO_3S$ 299.3427, found 299.3423.

**1-Trimethylsilylethoxymethyl-4-quinolone (5e) and 4-trimethylsilylethoxymethoxyquinoline (6b).** To a suspension of oil-free NaH (180 mg, 7.5 mmol) in dry THF (20 ml) cooled at -78 °C, 4-quinolone (1 g, 6.8 mmol) was added under $N_2$. The resulting mixture was stirred for 30 min and SEMCl (1.1 ml, 6.8 mmol) was added and the stirring was continued for 15 min at -20 °C and 24 h at rt. The organic solvent was evaporated and the residue was purified by flash column chromatography. On elution with $CH_2Cl_2$ the *O*-alkylated quinoline, **6b** (663 mg, 35%) was obtained: $^1$H-NMR ( 200 MHz, $CDCl_3$) δ 0.01 (s, 9H); 0.99 (t, *J* = 8.4 Hz, 2H); 3.84 (t, *J* = 8.4 Hz, 2H); 5.48 (s, 2H); 7.00 (d, *J* = 5.3 Hz, 1H); 7.51 (dd, *J* = 7.9 and 7.5 Hz, 1H); 7.70 (dd, *J* = 7.9 and 7.5 Hz, 1H); 8.07 (d, *J* = 7.9 Hz, 1H); 8.24 (d, *J* = 7.9 Hz, 1H); 8.76 (d, *J* = 5.3 Hz, 1H). MS (EI) 275 ($M^+$, 23), 217 (52), 202 (79), 158 (100). HRMS calcd for $C_{15}H_{21}NO_2Si$ 275.4219, found 275.4227. The subsequent fractions gave **5e** (996 mg, 53%) as an oil: $^1$H-NMR (200 MHz, $CDCl_3$) δ -0.04 (s, 9H); 0.93 (t, *J* = 8.2 Hz, 2H); 3.60 (t, *J* = 8.2 Hz, 2H); 5.44 (s, 2H); 6.25 (d, *J* = 7.7 Hz, 1H); 7.40-7.45 (m, 1H); 7.60 (d, *J* = 7.7 Hz, 1H); 7.67 (m, 2H); 8.44 (d, *J* = 7.9 Hz, 1H). $^{13}$C-NMR (50.3 MHz,

$CDCl_3$) δ 1.9 (q); 17.3 (t); 66.1 (t); 82.2 (t); 119.5 (d); 116.3 (d); 124.0 (d); 126.4 (d); 126.8 (s); 132.1 (d); 139.7 (s); 142.7 (d); 178.7 (s). MS (EI) 276 ($MH^+$, 4), 275 ($M^+$, 16), 217 (45), 158 (100). HRMS calcd for $C_{15}H_{21}NO_2Si$ 275.4219, found 275.4211.

**7-Oxo-5,7-dihydrofuro[3,4-*b*]pyridine 1-oxide (7b).** To a solution of pyridolactone **7a**[15] (1.0 g, 7.4 mmol) in AcOH (10 ml), 33% $H_2O_2$ (2.5 ml) was added, the mixture was stirred for 45 min at reflux temperature and after a second addition of $H_2O_2$ (2.5 ml) was refluxed for 3 h. The solution was cooled, the acetic acid was evaporated *in vacuum* and the resulting residue was purified by crystallisation from MeOH, giving **7b** (0.8 g, 70%) mp 233-235 °C: IR (KBr) 1770, 1430, 1365. $^1$H-NMR (200 MHz, DMSO-$d_6$) δ 5.34 (s, 2H); 7.52 (d, $J$ = 7.7 Hz, 1H); 7.67 (dd, $J$ = 7.7 and 6.3 Hz, 1H); 8.34 (d, $J$ = 6.3 Hz, 1H). $^{13}$C-NMR (50.3 MHz, $D_2O$) δ 71.2 (t); 128.0 (d); 134.3 (d); 134.9 (s); 143.6 (d); 150.5 (s); 170.5 (s). MS (CI) 152 ($MH^+$, 100), 136 (5). Anal. Calcd for $C_7H_7NO_7$: C, 55.63; H, 3.33; N, 9.27. Found: C, 55.16; H, 3.46; N, 9.41.

**1-Methoxycarbonyl-2-(7-oxo-5,7-dihydrofuro[3,4-*b*]pyridin-5-yl)-4-oxo-1,2,3,4-tetrahydroquinoline (8).** To a solution of **7a** (500 mg, 3.7 mmol) in dry THF (20 ml) cooled to -78 °C under $N_2$, LDA (2.5 ml, 3.7 mmol) was added, the mixture was stirred for 30 min then **5b** (760 mg, 3.7 mmol) was added. After 1 h at -78 °C and 5 h at rt, saturated aqueous $NaHCO_3$ was added and the organic solvent was evaporated *in vacuum* and the aqueous solution was extracted with $CH_2Cl_2$. The organic layer was dried and evaporated. The resulting residue was purified by column chromatography. On elution with $CH_2Cl_2$-MeOH (98:2) **8** (60 mg, 5%) was obtained: IR (Film) 1782, 1717, 1687, 1329. $^1$H-NMR (500 MHz, $CDCl_3$) δ 3.05 (dd, $J$ = 18.0 and 1.5 Hz, 1H); 3.26 (dd, $J$ = 18.0 and 7.0 Hz, 1H); 3.69 (s, 3H); 5.47 (m, 1H); 5.62 (d, $J$ = 5.5 Hz, 1H); 7.14 (ddd, $J$ = 7.7, 7.0 and 1.0 Hz, 1H); 7.15 (dd, $J$ = 7.0 and 1.0 Hz, 1H); 7.36 (ddd, $J$ = 7.2, 7.0 and 1.5 Hz, 1H); 7.5 (dd, $J$ = 7.7 and 4.5 Hz, 1H); 7.89 (ddd, $J$ = 7.7, 7.0 and 1.5 Hz, 1H); 7.94 (dd, $J$ = 7.7 and 1.5 Hz, 1H); 8.81 (dd, $J$ = 4.5 and 1.5 Hz, 1H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 40.0 (t); 53.8 (d); 55.1 (q); 80.8 (d); 123.9 (d); 125.0 (d); 126.8 (d); 127.0 (d); 131.9 (d); 134.6 (d); 153.1 (d); 185.2 (s). MS (CI, $CH_4$) 339 ($MH^+$, 100), 295 (26). HRMS calcd for $C_{18}H_{14}N_2O_5$ 338.0978, found 338.0909.

**General procedure for the preparation of 9a-c.** A solution of *N*-oxide **7b** (200 mg, 1.3 mmol) in dry DMSO (2 ml) was added to oil-free NaH (40 mg, 1.6 mmol) in dry DMSO (3 ml) under $N_2$ and then the quinolone **5b-d** (1.3 mmol) was added. The reaction mixture was stirred for 14 h at rt under $N_2$. The solvent was evaporated, $H_2O$ was added and the mixture was washed with $CH_2Cl_2$. The aqueous layer was evaporated in vacuum, the residue was dried and crystallized from $Me_2CO$.

**5,12-Dihydroxypyrido[2,3-*b*]acridine-2,11-dione (9a).** From **5b** (271 mg, 1.3 mmol), **9a** (30 mg, 10%) was obtained: IR (KBr) 3060, 1785, 1600. $^1$H-NMR (200 MHz, $D_2O$) δ 6.73 (d, $J$ = 6.8 Hz, 1H); 7.42 (dd, $J$ =10.0 and 8.0 Hz, 1H); 7.55 (d, $J$ = 10.0 Hz, 1H); 7.68 (dd, $J$ = 9.0 and 8.0 Hz, 1H); 7.97 (d, $J$ = 9.0 Hz, 1H); 8.25 (d, $J$ = 6.8 Hz, 1H). $^{13}$C-NMR ( 50.3 MHz, $D_2O$) δ 109.3 (d); 123.3 (d); 127.4 (d); 132.0 (d); 139.9 (d); 148.1 (d). MS (CI, $NH_3$) 308 ($MNH_4^+$, 100), 294 ($M^+$, 4), 223 (9), 232 (69).

**5,12-Dihydroxy-6-(2-methoxyethoxymethyl)pyrido[2,3-*b*]acridine-2,11-dione (9b).** From **5c** (303 mg, 1.3 mmol) **9b** (40 mg, 8%) was obtained: IR (KBr) 3000, 1780, 1575. $^1$H-NMR (200 MHz, $D_2O$) δ 3.05 (s, 3H); 3.25-3.32 (m, 2H); 3.38-3.40 (m, 2H); 5.31 (s, 2H); 6.10 (d, $J$ = 7.4 Hz, 1H); 7.16 (dd, $J$ = 8.0 and 7.0 Hz, 1H); 7.35-7.50 (m, 2H); 7.76 (d, $J$ = 8.0 Hz, 1H); 7.78 (d, $J$ = 7.4 Hz, 1H). $^{13}$C-NMR (50.3 MHz, $D_2O$) δ 60.8 (q); 70.5 (t); 73.4 (t); 86.0 (t);110.3 (d); 120.1 (d); 127.7 (d); 128.8 (d); 136.7 (d); 149.0 (d). MS (CI, $NH_3$) 383 ($MH^+$, 4), 320 (21), 169 (100), 153 (53).

**5,12-Dihydroxy-6-(*p*-toluensulfonyl)pyrido[2,3-*b*]acridine-2,11-dione (9c).** From **5d** (388 mg, 1.3 mmol), **9c** (40 mg, 8%) was obtained: IR (KBr) 3400, 1780, 1590. $^1$H-NMR (200 MHz, $D_2O$) δ 2.00 (s, 3H); 6.56 (d, *J* = 6.7 Hz, 1H); 6.90 (d, *J* = 9 Hz, 1H); 7.30 (m, 3H); 7.42 (d, *J* = 8.0 Hz, 2H); 7.58 (d, *J* = 10.0 Hz, 1H); 7.74 (d, *J* = 10.0 Hz, 1H); 8.18 (d, *J* = 6.7 Hz, 1H). $^{13}$C-NMR ( 50.3 MHz, $D_2O$) δ 23.3 (q); 107.8 (d); 122.1 (d); 126.2 (d); 128.1 (d); 130.8 (d); 132.1 (d); 137.7 (d); 146.9 (d). MS (CI, $NH_3$) 449 ($MH^+$, 1), 332 (2), 163 (100).

**1-Methyl-2-trimethylstannyl-4-quinolone (10).** To a solution of 1.5 M LDA (2.51 ml, 3.8 mmol) in dry THF (20 ml) at -78 °C a solution of **1a** (200 mg, 1.2 mmol) in dry THF (40 ml) was added very slowly (45 min) under $N_2$ then the mixture was stirred for 30 min. After this time $Me_3SnCl$ (1.5 ml, 1M in THF, 1.5 mmol) was added and the mixture was stirred at -78 °C for 1 h and for 5 h at rt. Saturated $NH_4Cl$ (10 ml) was added, the THF was evaporated *in vacuum* and the layer was extracted with $CH_2Cl_2$. The organic solution was dried and evaporated affording a residue which was purified by column chromatography. On elution with $CH_2Cl_2$ **10** (120 mg, 30%) was obtained, mp 182-184 °C ($CH_2Cl_2$). IR (Film) 1655, 1545, 1430. $^1$H-NMR (200 MHz, $CDCl_3$) δ 0.67 (s, 9H); 3.64 (s, 3H); 6.40 (s, 1H); 7.43-7.62 (m, 2H); 7.8 (d, J = 8.0 Hz, 1H); 8.5 (d, J = 8.5 Hz, 1H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ -0.7 (q); 36.0 (q); 112.4 (d); 115.8 (d); 124.8 (d); 127.0 (s); 127.1 (d); 133.3 (d); 141.2 (s); 143.9 (s); 177.4 (s). Anal. Caled for $C_{13}H_{17}NOSn.\ H_2O$: C, 45.92; H, 4.54; N, 4.12. Found: C, 45.60; H, 4.60; N, 4.33.

**5,7-Dihydro-5-hydroxy-7-oxo-6-phenylpyrrolo[3,4-*b*]pyridine (13).**[17] A solution of *N*-phenyl-2-pyridinecarboxamide (3.0 g, 15.2 mmol) in dry THF (20 ml) was added to BuLi (18.9 ml, 30.4 mmol) at -78 °C under $N_2$ and the mixture stirred for 1 h at that temperature. Dry DMF (2.34 ml, 30.4 mmol) was added, the cool bath was removed and the reaction mixture was stirred for 2 h at rt. After this time saturated aqueous $NaHCO_3$ was added and the organic solvent was evaporated *in vacuum*. The aqueous solution was extracted with $CH_2Cl_2$, the organic layer dried, and evaporated. Most of the product was obtained by acidification (pH 3.4) of the aqueous solution and collected by filtration of the precipitate. The precipitate and residue were combined and purified by column chromatography, elution with EtOAc-$C_6H_{14}$ (6:4) gave **13** (2.54 g, 73%): IR (KBr) 3500, 1708, 1603, 1382. $^1$H-NMR (300 MHz, DMSO-$d_6$) δ 6.56 (d, *J* = 10.0 Hz, 1H); 6.94 (d, *J* = 10.0 Hz, 1H); 7.26 (d, *J* = 7.4 Hz, 1H); 7.46 (dd, *J* = 8.0 and 7.4 Hz, 2H); 7.67 (dd, *J* = 7.7 and 4.7 Hz, 1H); 7.77 (d, *J* = 8.0 Hz, 2H); 8.13 (dd, *J* = 7.7 and 1.4 Hz, 1H); 8.80 (dd, *J* = 4.7 and 1.4 Hz, 1H). $^{13}$C-NMR (70.4 MHz, DMSO-$d_6$) δ 80.2 (d); 122.7 (d); 125.4 (d); 127.0 (d); 129.0 (d); 132.4 (d); 137.3 (s); 138.9 (s); 149.4 (s); 152.0 (d); 164.0 (s).

**Methyl 3-dimethoxymethyl-2-pyridinecarboxylate (14a).**[17] A mixture of **13** (2.0 g, 8.8 mmol) and $H_2SO_4$ (6 ml, 112.6 mmol) in MeOH (100 ml) was stirred at reflux temperature for 72 h. The cooled solution was basified with saturated $NaHCO_3$ and extracted with $CH_2Cl_2$. The organic layer was dried and evaporated to give a residue which was purified by column chromatography. On elution with $Et_2O$-$C_6H_{14}$ (3:2) the acetal **14a** (1.0 g, 54%) was obtained. IR (Film) 1735, 1574, 1449, 1426, 1300. $^1$H-NMR (300 MHz, $CDCl_3$) δ 3.39 (s, 6H,); 4.00 (s, 3H); 6.04 (s, 1H); 7.47 (dd, *J* = 8.0 and 4.7 Hz, 1H); 8.09 (dd, *J* = 8.0 and 1.7 Hz, 1H); 8.65 (dd, *J* = 4.7 and 1.7 Hz, 1H). $^{13}$C-NMR (70.4 MHz, $CDCl_3$) δ 52.8 (q); 54.1 (q); 99.7 (d); 125.5 (d); 134.6 (s); 135.6 (d); 147.7 (s); 148.9 (d); 166.6 (s). MS (EI) 211 ($M^+$, 10), 196 (40), 180 (83), 164 (91), 57 (100).

**Methyl 3-(phenyliminomethyl)-2-pyridinecarboxylate (14b).** A mixture of **13** (2.0 g , 8.8 mmol), MeOH (100 ml) and $H_2SO_4$ (6 ml, 112.6 mmol) was refluxed for 3 h. Saturated aqueous $NaHCO_3$ was added until the mixture was basic, then MeOH was evaporated and the aqueous solution was extracted with $CH_2Cl_2$.

The organic layer was dried and evaporated and the residue was purified by column chromatography. Elution with $CH_2Cl_2$-MeOH (99:1) gave imine **14b** (1.1 g, 51%): IR (KBr) 1706, 1603, 1502, 1382. $^1$H-NMR (300 MHz, $CDCl_3$) δ 2.95 (s, 3H); 6.52 (s, 1H); 7.27 (ddd, *J* = 8.2, 7.5 and 1.0 Hz, 1H); 7.47 (dd, *J* = 8.2 and 7.5 Hz, 2H); 7.55 (dd, *J* = 7.7 and 5.0 Hz, 1H); 7.82 (dd, *J* = 8.2 and 1.0 Hz, 2H); 8.00 (dd, *J* = 7.7 and 1.5 Hz, 1H); 8.90 (dd, *J* = 5.0 and 1.5 Hz, 1H). $^{13}$C-NMR (70.4 MHz, $CDCl_3$) δ 49.6 (q); 85.2 (d); 121.7 (d); 125.8 (d); 126.4 (d); 129.2 (d); 131.8 (d); 133.9 (s); 136.6 (s); 150.8 (s); 153.0 (d); 164.6 (s). MS (EI) 240 ($M^+$, 77), 225 (79), 209 (100), 181 (60). Anal. Calcd for $C_{16}H_{12}N_2O_2$: C, 68.98; H, 5.04; N, 11.66. Found: C, 68.50; H, 5.69; N, 11.75.

**Methyl 3-formyl-2-pyridinecarboxylate (11b).** *p*-Toluenesulfonic acid (2.16 g, 11.4 mmol) was added to a solution of **14a** (2.0 g, 9.5 mmol) in $Me_2CO$ (50 ml) and the reaction mixture was stirred at reflux temperature for 3 h. The solvent was evaporated under vacuum, $CH_2Cl_2$ was added and the resulting solution was washed with saturated $NaHCO_3$. The organic layer was dried and evaporated to afford a residue which was purified by column chromatography. Elution with $C_6H_{14}$: $Et_2O$ (7:3) gave **11b** (1.0 g, 64%): IR (KBr) 1715, 1694, 1578, 1312. $^1$H-NMR ($CDCl_3$, 300 MHz) δ 4.09 (s, 3H); 7.66 (dd, *J* = 8.0 and 4.7 Hz, 1H); 8.31 (dd, *J* = 8.0 and 1.7 Hz, 1H); 8.88 (dd, *J* = 4.7 and 1.7 Hz, 1H); 10.67 (s, 1H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 53.4 (q); 126.6 (d); 132.8 (s); 136.5 (d); 149.1 (s); 152.7 (d); 165.2 (s); 190.4 (s). MS (EI) 165 ($M^+$, 1), 134 (6), 107 (20), 79 (100). HRMS calcd for $C_8H_7NO_3$ 165.1476, found 165.1450.

**5,12-Dihydroxy-6-methylpyrido[2,3-*b*]acridone (15a) and 7,12-dihydro-13-hydroxy-7-methyl-12-oxopyrido[2',3':5,6]oxepino[2,3-*b*]quinoline (16a).** A solution of **5a** (481 mg, 3.0 mmol) in dry THF (120 ml) was added slowly (45 min) to a solution of LDA (6 ml, 9.0 mmol) in dry THF (30 ml) cooled at -78 °C under $N_2$ and the solution was stirred at this temperature for 30 min. A solution of **11b** (500 mg, 3.0 mmol) in dry THF (20 ml) was added and the resulting mixture was stirred for 1 h at -78 °C and 5 h at rt. Saturated aqueous $NH_4Cl$ was added, the organic solvent was evaporated *in vacuum* and the aqueous solution was extracted with $CH_2Cl_2$. The organic layer was dried and evaporated to give a residue which was purified by flash column chromatography. On elution with $C_6H_{14}$:$CH_2Cl_2$ (20:80) the tetracyclic compound **15a** (50 mg, 5%) was obtained: $^1$H-NMR (200 MHz, $CDCl_3$) δ 4.22 (s, 3H); 7.24 (dd, *J*= 8.0 and 1.7 Hz, 1H); 7.34 (dd, *J* = 8.4 and 4.2 Hz, 1H); 7.45 (d, *J* = 8.4 Hz, 1H); 7.21 (ddd, *J* = 8.4, 8.4 and 1.7 Hz, 1H); 8.38 (dd, *J* = 8.0 and 1.8 Hz, 1H); 8.75 (dd, *J* = 8.4 and 1.7 Hz, 1H); 8.89 (dd, *J* = 4.2 and 1.7 Hz, 1H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 56.3 (q); 116.4 (d); 120.6 (d); 122.1 (d); 127.7 (d); 134.6 (d); 135.0 (d); 153.8 (d); 178.2 (s). MS (EI) 292 ($M^+$, 84), 263 (26), 235 (63), 69 (100). Anal. Calcd for $C_{17}H_{12}N_2O_3$.1/2 $H_2O$: C, 67.76; H, 4.01. Found: C, 67.50; H, 4.01. The following fractions gave hydroxy-oxepine **16a** (140 mg, 10%) mp 230-235 °C (*i*$Pr_2O$): IR (KBr ) 3250, 1648, 1607. $^1$H-NMR (500 MHz, $CDCl_3$) δ 4.23 (s, 3H); 7.24 (dd, *J* = 7.8 and 7.0 Hz, 1H); 7.39 (dd, *J* = 8.4 and 4.2 Hz, 1H); 7.50 (d, *J* = 8.7 Hz, 1H); 7.30 (ddd, *J* = 8.7, 7.0 and 1.5 Hz , 1H); 8.35 (dd, *J* = 8.4 and 1.5 Hz, 1H); 8.45 (dd, *J* = 7.8 and 1.5 Hz, 1H); 8.60 (s, 1H); 8.85 (dd, *J* = 4.2 and 1.5 Hz, 1H). $^{13}$C-NMR (70.4 MHz, $CDCl_3$) δ 39.8 (q); 115.4 (d); 117.0 (d); 117.0 (s); 120.6 (d); 120.8 (d); 122.6 (s); 125.2 (s); 127.6 (d); 134.7 (d); 138.2 (d); 138.5 (s); 140.1 (s); 146.3 (s); 150.4 (d); 179.4 (s). MS (EI) 292 ($M^+$, 3); 277 (20); 276 (67); 260 (46). Anal. Calcd for $C_{17}H_{12}N_2O_3$: C, 69.85; H, 4.14; N, 9.58. Found: C, 68.83; H, 4.43; N, 9.35.

**5,12-Dihydroxy-6-(2-methoxyethoxymethyl)pyrido[2,3-*b*]acridine (15b) and 7,12-dihydro-13-hydroxy-7-(2-methoxyethoxymethyl)-12-oxopyrido[2',3':5,6]oxepino[2,3-*b*]quinoline (16b).** To a solution of **5c** (706 mg, 3.0 mmol) in dry THF (40 ml) cooled to -78 °C, 1.5 M LDA (6 ml, 9.0

mmol) under $N_2$ was added and the mixture was stirred for 30 min at rt. A solution of **11b** (500 mg, 3.0 mmol) in dry THF (20 ml) was added, the mixture was stirred at -78 °C for 1 h and for 5 h at rt. Saturated aqueous $NH_4Cl$ was added and the organic solvent was evaporated. The aqueous layer was extracted with $CH_2Cl_2$. The organic solution was dried and evaporated to give a residue which was purified by flash column chromatography. Elution with $CH_2Cl_2$ gave **15b** (170 mg, 15%) mp 198-201 °C ($Et_2O$) IR (KBr) 3390, 1620 . $^1$H-NMR (200 MHz, $CDCl_3$) δ 3.35 (s, 3H); 3.56 (t, *J* = 4.5 Hz, 2H); 3.81 (t, *J* = 4.5 Hz, 2H); 6.10 (s, 2H); 7.25 (dd, *J* = 8.0 and 8.0 Hz, 1H); 7.36 (dd, *J* = 4.5 and 8.0 Hz, 1H); 7.70 (ddd, *J* = 8.8 and 1.5 Hz, 1H); 7.76 (d, *J* = 8 Hz, 1H); 8.34 (dd, *J* = 8.0 and 1.5 Hz, 1H); 8.73 (dd, *J* = 8, and 1.5 Hz, 1H); 8.87 (dd, *J* = 4.5 and 1.5 Hz, 1H); 15.34 (s, 1H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 59.0 (q); 67.0 (t); 71.8 (t); 80.0 (t); 107.0 (s); 114.0 (s); 116.5 (d); 118.6 (d); 120.2 (s); 121.7 (d); 125.1 (s); 126.3 (d); 129.5 (s); 133.2 (d); 135.3 (d); 140.0 (s); 145.2 (s); 152.0 (d); 155.1 (s); 184.7 (s). FABMS 367 ($MH^+$, 33); 366 ($M^+$, 72); 290 (100); 280 (70); 276 (90). UV (MeOH), λ (log ε) 240 (4.82), 2.77 (4.56), 330 (4.08), 4.15 (3.91) nm. Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.91; H, 5.33; N, 7.98. The following fractions afforded **16b** (220 mg, 20%) mp 220-222 °C (*i*$Pr_2O$). IR ( KBr) 3280, 1161, 1606, 1472. $^1$H-NMR (500 MHz, $CDCl_3$) δ 3.35 (s, 3H); 3.56 (t, *J* = 4.5 Hz, 2H); 3.81 (t, *J* = 4.5 Hz, 2H); 6.11 (s, 2 H); 7.26 (ddd, *J* = 8.0, 7.0 and 1.0 Hz, 1H); 7.41 (dd, *J* = 8.2 and 4.5 Hz, 1H); 7.70 (ddd, *J* = 8.5, 7.0 and 1.5 Hz, 1H); 7.82 (dd, *J* = 8.5 and 1.0 Hz, 1H); 8.34 (dd, *J* = 8.2 and 1.5 Hz, 1H); 8.41 (dd, *J* = 8.0 and 1.5 Hz, 1H); 8.61 (s, 1H); 8.86 (dd, *J* = 4.5 and 1.5 Hz, 1H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 58.9 (q); 66.9 (t); 71.7 (t); 79.9 (t); 116.8 (d); 117.2 (d); 118.1 (s); 120.7 (d); 121.8 (d); 122.6 (s); 124.6 (s); 127.0 (d); 134.6 (d); 137.7 (d); 138.5 (s); 139.6 (s); 145.2 (s); 150.4 (d); 179.5 (s); MS (EI) 366 ($M^+$, 1), 274 (98), 273 (100). UV (MeOH), λ (log ε) 214 (4.16), 238 (4.28), 271 (3.89), 333 (3.59) nm. Anal. Calcd for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.34; H, 5.12; N, 7.72.

**2-(*N*-Diethylcarbamoyl)pyridin-3-yl 1,4-dihydro-1-methyl-4-oxo-2-quinolinyl carbinol (17a).** To a solution of *N,N*-diethyl-2-pyridinecarboxamide (1.0 g, 5.6 mmol) in dry THF (50 ml) at -78 °C 1.3 M *s*-BuLi (5.2 ml, 6.7 mmol) was added under $N_2$, and then 2-formyl-1-methyl-4-quinolone[18] (1.26 g, 6.0 mmol) in THF (10 ml). The resulting mixture was stirred for 2 h at -78°C. After this time a second addition of 1.3 M *s*-BuLi (5.2 ml, 6.7 mmol) was made and stirring continued for 1 h at -78°C and 16 h at rt. Saturated aqueous $NH_4Cl$ was added, the organic solvent was evaporated *in vacuum* and the residue was extracted with $CH_2Cl_2$. The organic layer was dried and evaporated to give a residue which was purified by column chromatography. On elution with $CH_2Cl_2$:MeOH (98: 2) **17a** was obtained (0.5 g, 25%): IR (Film): 3200, 1621, 1601. $^1$H-NMR (200 MHz, $CDCl_3$) δ 0.99 (t, J = 7.0 Hz, 3H); 1.14 (t, J = 7.0 Hz, 3H); 2.95-3.2 (m, 4H); 3.58 (s, 3H); 6.33 (s, 1H); 6.38 (s, 1H); 7.2-7.4 (m, 3H); 7.54 (ddd, J = 8.0, 8.0 and 1.6 Hz, 1H); 7.83 (dd, J = 8.0 and 1.4 Hz, 1H); 8.25 (dd, J = 8.0 and 1.6 Hz, 1H); 8.51 (dd, J = 4.8 and 1.4 Hz, 1H). $^{13}$C-NMR (70.4 MHz, $CDCl_3$) δ 12.1 (q); 13.5 (q); 34.6 (q); 39.2 (t); 43.1 (t); 68.2 (d); 111.0 (d); 115.5 (d); 123.5 (d); 124.0 (d); 125.7 (s); 125.9 (d); 132.4 (d); 133.7 (s); 135.6 (d); 141.5 (s); 147.9 (d); 153.4 (s); 155.2 (s); 168.0 (s); 177.9 (s). MS (EI) 365 ($M^+$, 55), 348 (18), 293 (80), 235 (100). HRMS calcd for $C_{21}H_{23}N_3O_3$ 365.4307, found 365.4320.

**2-(*N*-Phenycarbamoyl)pyridin-3-yl 1,4-dihydro-1-methyl-4-oxo-2-quinolinyl carbinol (17b).** To a solution of *N*-phenyl-2-pyridinecarboxamide (1.0 g, 5.0 mmol) in dry THF (50 ml) at -78 °C 1.6 M BuLi (6 ml, 10.0 mmol) was added and the mixture was stirred for 1 h. A solution of 2-formyl-1-methyl-4-quinolone[18] (944 mg, 5.0 mmol) in dry THF (10 ml) was added and the mixture was stirred for 1 h at -78 °C and 16 h at rt.

Saturated aqueous $NH_4Cl$ was added, the organic solvent was eveporated *in vacuum* and the residue was extracted with $CH_2Cl_2$. The organic layer was dried and evaporated giving a residue which was purified by column chromatography. On elution with $CH_2Cl_2$: MeOH (98:2) **17b** was obtained (0.6 g, 30%):IR (Film): 3300, 1621, 1599, 1559. $^1$H-NMR (300 MHz, DMSO-$d_6$) δ 3.96 (s, 3H); 5.48 (s, 1H); 7.00 (s, 1H); 7.05 (ddd, J = 7.5, 7.5 and 1.0 Hz, 1H); 7.27 (ddd, J = 8.5, 8.0 and 1.0 Hz, 2H); 7.36 (ddd, J = 7.5, 7.3 and 1.0 Hz, 1H); 7.68 (dd, J = 8.0 and 1.5 Hz, 2H); 7.75 (ddd, J = 8.5, 8.5 and 1.5 Hz, 1H); 7.78 (dd, J = 8.0 and 4.5 Hz, 1H); 7.86 (d, J = 7.3 Hz, 1H); 8.09 (dd, J = 8.0 and 1.5 Hz, 1H); 8.27 (dd, J = 8.0 and 1.5 Hz, 1H); 8.74 (dd, J = 4.5 and 1.5 Hz, 1H); 10.7 (s, 1H). $^{13}$C-NMR (70.4 MHz, DMSO-$d_6$) δ 34.4 (q); 67.1 (d); 108.8 (d); 117.1 (d); 120.5 (d); 123.4 (d); 124.2 (d); 125.5 (d); 126.2 (s); 126.8 (d); 128.8 (d); 132.6 (d); 137.1 (d); 138.3 (s); 142.0 (s); 147.1 (s); 147.7 (d); 156.5 (s); 164.0 (s); 176, 3 (s). MS (EI): 385 ($M^+$, 8), 354 (22), 292 (11), 263 (47), 235 (100). HRMS calcd for $C_{23}H_{19}N_3O_3$ 385.4211, found 385.4203.

**5,6,11,12-Tetrahydro-6-methyl-5,11,12-trioxopyrido[2,3-*b*]acridine (18a).** A solution of CAN (750 mg, 1.4 mmol) in $H_2O$ (2 ml) was added to a solution of **15a** (200 mg, 0.7 mmol) in MeCN (6 ml). The reaction mixture was stirred for 15 min at rt and $H_2O$ (15 ml) was added. The resulting mixture was extracted with $CH_2Cl_2$. The organic layer was dried and evaporated to give the quinone **18a** (180 mg, 90%) mp 210-212 °C (*i*$Pr_2O$). IR (KBr) 1700, 1668, 1593 . $^1$H-NMR (500 MHz, $CDCl_3$) δ 4.13 (s, 3H); 7.51 (ddd, *J* = 8.0, 8.0 and 1.0 Hz, 1H); 7.71 (d, *J* = 8.5 Hz, 1H); 7.73 (dd, *J* = 8.0 and 4.5 Hz, 1H); 7.80 (ddd, *J* = 8.5, 8.0 and 1.5 Hz, 1H); 8.51 (dd, *J* = 8.0 and 1.5 Hz, 1H); 8.55 (dd, *J* = 8.0 and 1.5 Hz, 1H); 9.00 (dd, *J* = 4.5 and 1.5Hz, 1H). $^{13}$C-NMR (50.3 MHz, $CDCl_3$) δ 40.2 (q); 117.5 (d); 126.3 (d); 127.7 (d); 128.9 (d); 129.9 (s); 134.2 (d); 135.1 (d); 140.5 (s); 141.8 (s); 148.5 (s); 148.8 (s); 154.3 (d); 178.9 (s); 179.6 (s); 182.9 (s). MS (EI) 292 ($M^+$, 60), 277 (100). Anal. Calcd for $C_{17}H_{10}N_2O_3$: C, 70.34; H, 3.47; N, 9.65. Found: C, 71.014; H, 3.69; N, 9.62.

**5,12-Dihydro-11-hydroxy-5,12-dioxopyrido[2,3-*b*]acridine (18c) and 5,6,11,12-Tetrahydro-6-(2-methoxyethoxymethyl)-5,11,12-trioxopyrido[2,3-*b*] acridine (18b).** A solution of CAN (600 mg, 1.1 mmol) in $H_2O$ (2 ml) was added to a solution of **15b** (200 mg, 0.54 mmol) in MeCN (6 ml) and the mixture was stirred for 15 min at rt, then $H_2O$ (15 ml) was added and the solution was extracted with $CH_2Cl_2$. The organic solution was dried and evaporated *in vacuum* to afford a residue which was purified by column chromatography. Elution with $CH_2Cl_2$: MeOH gave **18c** (274 mg, 90%) mp 210-213 °C (MeOH). IR (KBr) 3428, 1662, 1627, 1614. $^1$H-NMR ( 500 MHz, DMSO-$d_6$) δ 7.49 (ddd, *J* = 8.5, 7.5 and 1.0 Hz); 7.79 (ddd, *J* = 8.0, 7.5 and 1.5 Hz, 1H); 7.91 (dd, *J* = 8.0 and 4.5 Hz, 1H); 8.14 (dd, *J* = 8.0 and 1.0 Hz, 1H); 8.20 (dd, *J* = 8.0 and 1.5 Hz, 1H); 8.48 (dd, *J* = 8.0 and 1.5 Hz, 1H); 9.01 (dd, *J* = 4.5 and 1.5 Hz, 1H); 12.50 (s, 1H). $^{13}$C-NMR (70.4 MHz, $CDCl_3$) δ 111.8 (s); 120.6 (d); 125.7 (d); 125.8 (d); 128.8 (s); 129.1 (d); 130.7 (s); 133.4 (d); 134.6 (d); 138.0 (s); 144.5 (s); 146.7 (s); 153.4 (d); 174.8 (s); 179.1 (s); 179.4 (s). FABMS 276 ($M^+$, 100), 231 (17), 220 (24), 206 (30). Anal. Calcd for $C_{16}H_8N_2O_3$. 1/2$H_2O$: C, 68.66 H, 3.19; N, 9.85. Found: C, 68.55; H, 3.08; N, 9.75. When a reaction time of 5 min was used, **18b** (26%) was obtained: $^1$H-NMR (200 MHz, $CDCl_3$) δ 3.20 (s, 3H); 3.52 (m, 2H); 3.80 (m, 2H); 6.00 (s, 2H); 7.51 (ddd, J = 11.0, 10.5 and 2.0 Hz, 1H); 7.73-7.82 (m, 2H, H-3); 7.94 (d, J = 12.6 and 2.0 Hz, 1H); 8.47 (dd, J = 11.0 and 1.0 Hz, 1H); 8.58 (dd, J = 13.5 and 2.0 Hz, 1H); 9.04 (dd, J = 7.0 and 2.0 Hz, 1H); $^{13}$C-NMR (70.4 MHz, $CDCl_3$) δ 58.9 (q); 68.4 (t); 72.1 (t); 79.7 (t); 118.9 (d); 126.3 (d); 127.2 (d); 128.8 (d,); 133.9 (d); 135.0 (d); 154.3 (d); 180.0 (s).

**13-Chloro-7,12-dihydro-12-oxopyrido[2',3':5,6]oxepino[2,3-*b*]quinoline (19).** To a solution of **17a** (500 mg, 1.3 mmol) in THF (16 ml) and MeOH (7 ml) a solution of LiOH (164 mg, 3.9 mmol) in $H_2O$ (10 ml) was added and the mixture was refluxed for 24 h. 1N HCl was added until the solution was acidic and the solvent was removed *in vacuum*. The residue was dried in a vacuum oven at 50°C. The solid material was dissolved in $SOCl_2$ (5 ml) and the solution refluxed for 4 h. The $SOCl_2$ was removed *in vacuum* and the residue was partitioned between $CH_2Cl_2$ and saturated aqueous $NaHCO_3$. The organic layer dried and evaporated gave a residue which was purified by column chromatography. On elution with $CH_2Cl_2$ **19** was obtained (100 mg, 23%): IR (Film): 1813, 1496, 1327. $^1$H-NMR (500 MHz, $CDCl_3$) δ 7.65 (ddd, J = 8.5, 7.0 and 1.0 Hz, 1H); 7.68 (dd, J = 8.5 and 4.5 Hz, 1H); 7.75 (ddd, J = 7.5, 7.0 and 1.0 Hz, 1H); 8.01 (dd, J = 8.5 and 1.0 Hz, 1H); 8.09 (s, 1H); 8.20 (dd, J = 7.5 and 1.0 Hz, 1H); 8.70 (dd, J = 8.5 and 1.5 Hz, 1H); 8.93 (dd, J = 4.5 and 1.5 Hz, 1H). $^{13}$C-NMR (70.4 MHz, $CDCl_3$) δ 118.0 (d); 124.2 (d); 128.0 (d); 129.0 (d); 130.0 (d); 131.2 (d); 135.0 (d); 154.3 (d). MS (EI) 295 ($M^+$, 100), 267 (77), 252 (69), 239 (28).

**Preparation of 15a by cyclization of 17a.** A solution of **17a** (100 mg , 0.3 mmol) in $POCl_3$ (5ml) was refluxed for 1 h. After this time the $POCl_3$ was removed *in vacuum* and the residue was dissolved in $CH_2Cl_2$. The organic solution was washed with saturated aqueous $NaHCO_3$, dried and evaporated to give a residue which was purified by column chromatography. Elution with $CH_2Cl_2$ afforded **15a** (10 mg, 11%) identical with material prepared as described above.

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