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Synthesis and Reactivity of a N-Aryl-2-vinyltetrahydro-4-oxoquinoline

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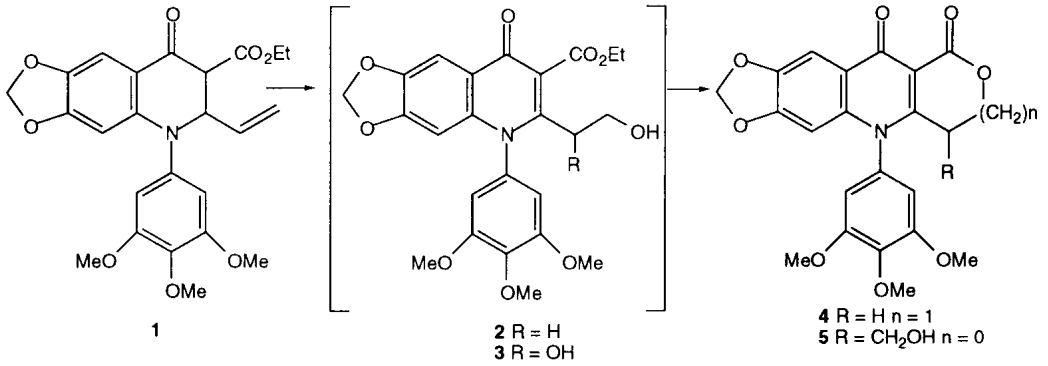
Abstract : Ethyl 2-ethenyl-6,7-methylenedioxy-1,2,3,4-tetrahydro-1-(3',4',5'-trimethoxyphenyl)-4-oxoquinoline-3-carboxylate **1** was prepared by the reaction of vinylcuprate on ethyl 1,4-dihydro-6,7-methylenedioxy-1-(3',4',5'-trimethoxyphenyl)-4-oxoquinoline-3-carboxylate **9**. Different quinolones and a tetrahydro-4-oxoquinoline have been obtained by oxidation of **1**. Depending on the reagent, the initial addition occurs either at only one of the reactive functions, namely the vinyl double bond or the enolate, or at both. New unexpected 1,2-dihydroquinolines were synthesized in attempts at protecting the diol obtained by reduction of **1**.

In a previous study dealing with the preparation of N-arylquinolones annelated to either a 5-membered or 6-membered lactone, designed as hybrids of antibacterial 4-quinolones and antitumor epipodophyllotoxin, we described the synthesis of δ- and γ-quinolone-lactones **4** and **5** by lactonization of the intermediates **2** and **3**.[1] The latters have been obtained from **1** by concomitant oxidation of the heterocyclic ring and transformation of the vinyl group into a mono- or di-hydroxylated chain (Scheme 1).



SCHEME 1

The quinolone-γ-lactone **5** was prepared in a one pot reaction but in poor yield (20%) by reaction of $KMnO_4$ with **1**. In order to optimize this reaction, **1** was treated with other reagents. Then, it appeared that **1** might undergo various transformations depending on the oxidative reagent.

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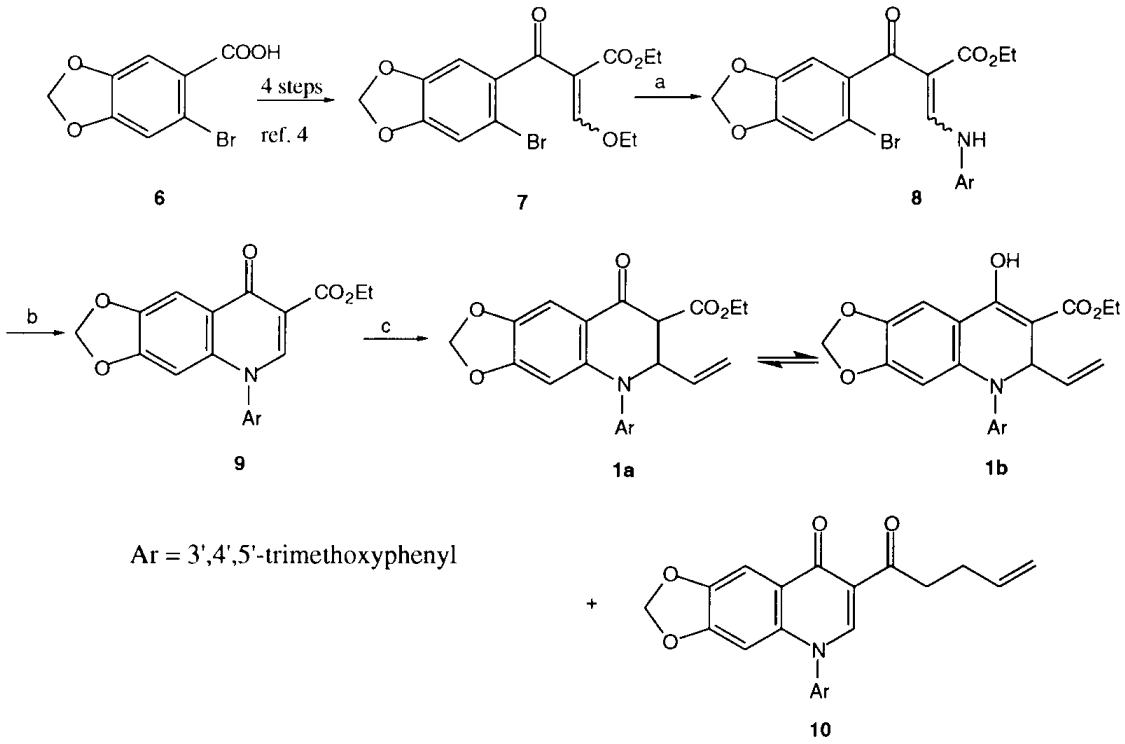
In the present paper, we describe the synthesis of the key derivative **1** and its chemical unexpected reactivity towards different reagents.

RESULTS AND DISCUSSION

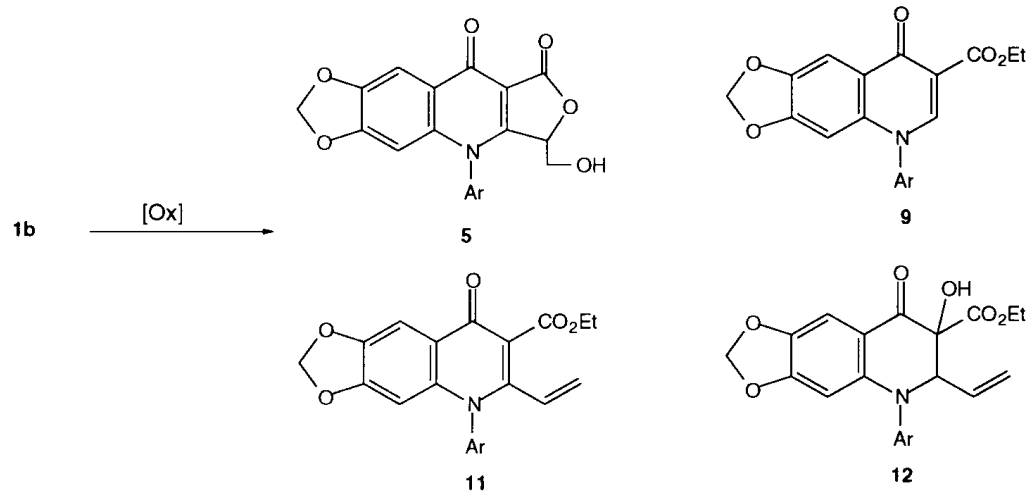
The synthesis of **1** is described in Scheme 2. 2-Bromo-4,5-methylenedioxybenzoic acid **6** prepared from piperonal,[2] was transformed into the ketoester **7**[3] following the synthesis described for 2-chloro-4,5-methylenedioxybenzoic acid.[4] The condensation of **7** with 3,4,5-trimethoxyaniline afforded the enamine **8**, which was cyclized into **9** in 90% yield by heating in DMF at 110°C in the presence of K_2CO_3 according to the procedure described by Chu *et al.* [5] Introduction of the vinyl side chain was achieved by reacting **9** with vinyl cuprate.[6] Alkylated product **1** was obtained in 62% yield as a mixture of keto-ester **1a** and enol ester **1b** along with **10** (24%), an undesired product resulting from 1,2-addition of vinylmagnesium bromide to the ester function of **9** followed by a 1,4-addition of a molecule of vinylcuprate to the resulting vinyl ketone. The value of $J_{H\text{-}2,H\text{-}3}$ (J = 4.6 Hz) for **1a** does not allow the determination of the *cis* or *trans* relative relationship between the vinyl chain and the ester group.



a) 3,4,5-Trimethoxyaniline, EtOH, rt, 12 h. b) K_2CO_3, DMF 110°C, 5 h. c) Vinylmagnesium bromide, CuI, THF, -70°C to -40°C, 5 h.

SCHEME 2

In order to prepare lactones by cyclisation of the dihydroxylated intermediate **3**, compound **1** was treated with $KMnO_4$. When the reaction was started at 0°C and then pursued at 20°C in an acetone-water mixture, compound **9** was obtained as the major product (75%) with only a small amount (20%) of the desired compound **5** (Scheme 3, Entry 1). At reflux in the same solvents (Scheme 3, Entry 2), no formation of lactone **5** was observed but **9** and **11** were isolated in 40 and 44% yield.



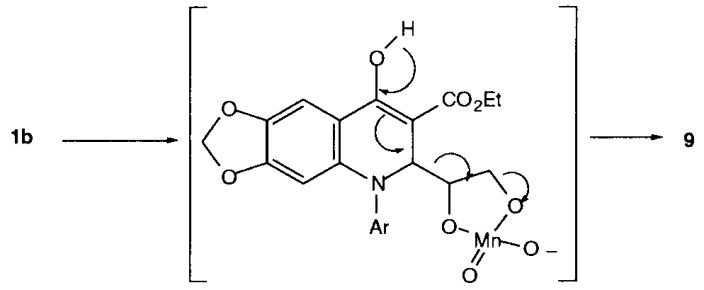
Entry	Conditions	5	9	11	12
1	$KMnO_4$, acetone/H_2O, 0°C-20°C, 36 h	20%	75%	-	-
2	$KMnO_4$, acetone/H_2O, reflux, 4 h	-	40%	44%	-
3	NMO, acetone/H_2O, OsO_4 2‰, rt, 36 h	-	31%	33%	35%
4	OsO_4, *t*-butanol/H_2O, rt, 36 h	-	32%	33%	33%
5	MnO_2, MeOH, 50°C, 3 h	-	-	-	68%
6	$NaIO_4$/$KMnO_4$, H_2O/EtOH, rt, 2 h	-	-	-	70%
7	*m*-CPBA, $CHCl_3$, rt, 2 h	-	-	-	75%
8	Jones reagent/OsO_4 (cat), acetone, rt, 20 h	-	-	60%	-

SCHEME 3

The structure of **5** was deduced from the ^1H NMR spectrum by the disappearance of the signals of the ethoxy group and the vinyl chain and by the appearance of an ABX system (δ : 3.00, 3.61 and

5.40 ppm). The two shielded protons of this system were coupled with a triplet (δ 5.11 ppm) which disappeared upon addition of D_2O indicating the presence of a hydroxymethyl side chain. The ^{13}C NMR spectrum of **5** showing a methine signal at δ 78.89 ppm and a methylene signal at δ 59.85 ppm confirmed the proposed structure. Compound **5** is one of the two possible lactones that could be obtained by cyclization of the intermediate diol **3** resulting from the dihydroxylation of the vinyl chain of **1** and oxydation into a quinolone ring. The formation of the six-membered lactone was not observed under these conditions.

The formation of **9** is rather intriguing. It could result from the cleavage of cyclic manganate ester **13** (Scheme 4).



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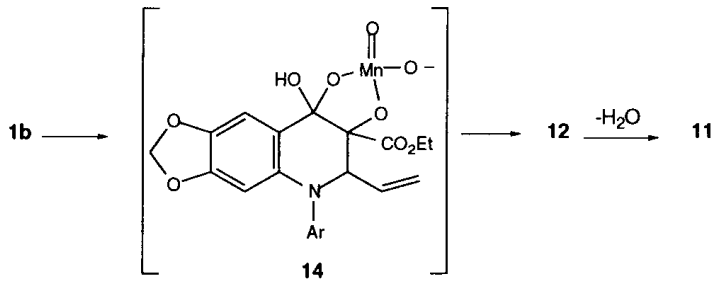
SCHEME 4

Formation of **11** could be explained by the fact that the cyclic manganate ester is not formed at the vinylic double bond but at the 3,4-positions of **1** followed by dehydration of the 3-hydroxy intermediate **14** (Scheme 5).



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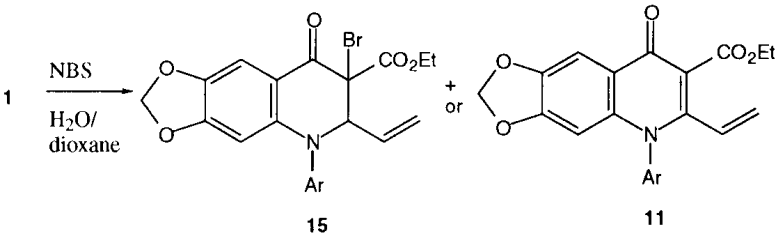
SCHEME 5

With these rather surprinsing results in hand, we decided to investigate the reactivity of **1** towards various oxidative reagents. N-methylmorpholine-N-oxide (NMO) in the presence of a catalytic amount of OsO_4[7] (Entry 3) and OsO_4 alone (Entry 4) were choosen as dihydroxylation reagents ; $NaIO_4$-$KMnO_4$[8] (Entry 6), Jones reagent, OsO_4 (cat)[9] (Entry 8) as oxidative cleavage reagents ; and then MnO_2 (Entry 5) as nitrogen heterocyclic nucleus oxidant. The results are indicated in Scheme 3.

When either NMO/OsO_4 or OsO_4 alone were used, a 1/1/1 mixture of **9**, **11**, **12** was obtained (Entries 3,4). In contrast with the $KMnO_4$ reaction, the 3-hydroxy derivative **12** was isolated. It exists as a single isomer but the stereochemistry of the quaternary center has not been determined. When the oxidation was performed with MnO_2 in methanol, $NaIO_4$-$KMnO_4$, or *m*-CPBA in $CHCl_3$[10], **12** was obtained alone in 68%-75% (Entries 5,6,7). Jones reagent/OsO_4 (cat) (Entry 8) gave only quinolone **11** in 60% yield.

Another example of the C-3 or enol reactivity and facile subsequent oxidation into quinolone is observed when using hydroxy-bromation conditions of the vinyl chain.[11] When the reaction was performed at room temperature, a mixture of C-3 bromo derivative **15** and quinolone **11** was obtained in 42% and 30% yield respectively (Scheme 6). At refluxing condition only quinolone **11** (60%) was isolated from the reaction mixture.

All these results could be interpreted in term of reactivity of the major tautomeric form **1b**.

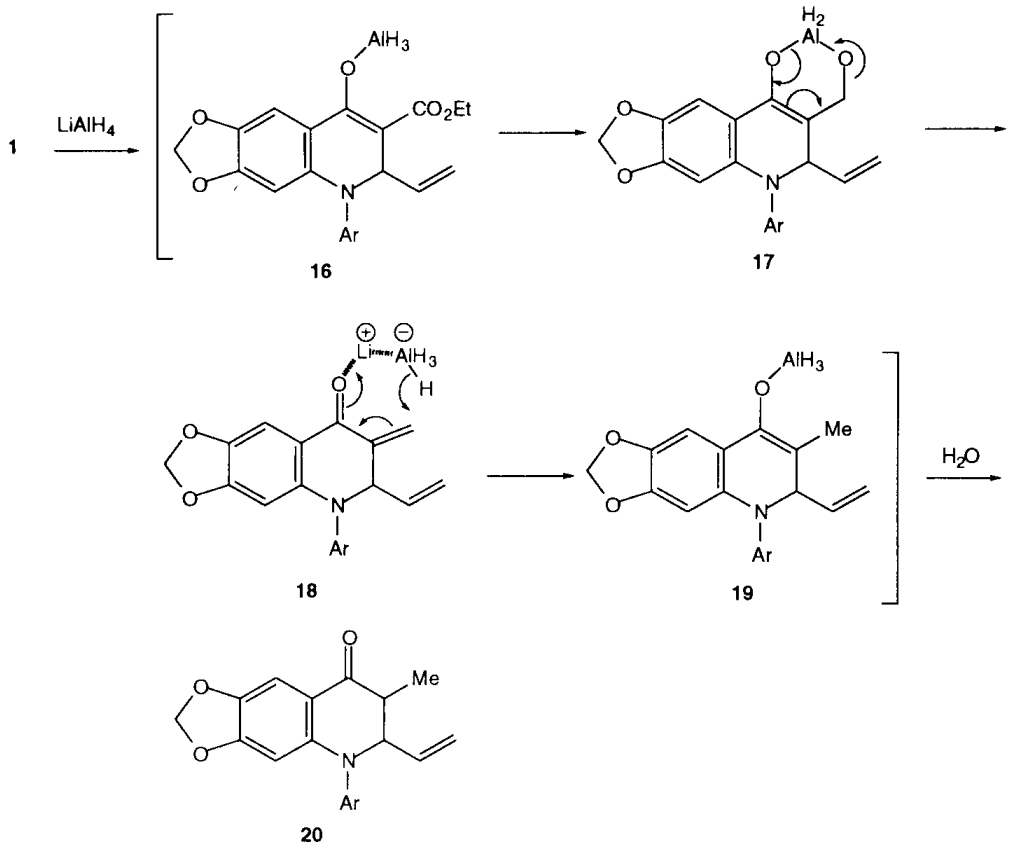


SCHEME 6

In another series of experiments, we have investigated the reactivity of **1** towards hydrides.

Our first experiment (Scheme 7) was conducted with $LiAlH_4$ in refluxing THF. In these conditions only ketone **20** was obtained in 69% yield as a single epimer whose ^{1}H-NMR measurement of $J_{H\text{-}2,H\text{-}3}$ value (J = 5.6 Hz) did not allow the determination of stereochemistry. This unexpected product could result from a retro-Michael reaction on **17** followed by a 1,4-reduction of resulting enone **18**. This result is rather surprizing as it is known that $LiAlH_4$ predominantly reduces, on the one hand, the carbonyl function in presence of ester and, on the other hand, the carbonyl group of an enone.[12]

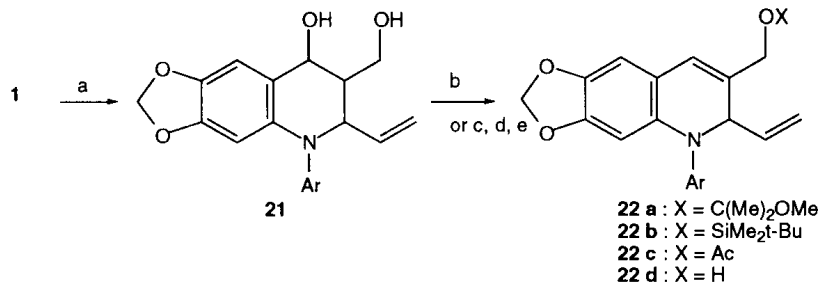
The relative stability of enol **1b** could justify the occurence of the first reduction of **1** into **18**. The 1,4-reduction could be interpreted by the δ-*cis* geometry of the enone **18** that drives to the formation of a six-membered intermediate.



SCHEME 7

When $NaBH_4$ was used as a reducing agent, diol **21** was obtained in 47% yield as a mixture of two isomers in a 2/1 ratio (Scheme 8). The major isomer was obtained pure by crystallization from acetone. The coupling constants of the former ($J_{H\text{-}2,H\text{-}3}$ = 4.8 Hz and $J_{H\text{-}2,H\text{-}4}$ = 4.0 Hz) allowed us to propose a all *cis* relative stereochemistry. To try to confirm this hypothesis, preparation of **21** derivatives was envisaged.

Attempt at protecting the diol function by reaction with 2,2-dimethoxypropane in presence of APTS led exclusively to 1,2-dihydroquinoline **22a** by dehydration and protection of the primary alcohol. Similar results were observed by reaction with other protecting groups (TBDMS, Ac, $PhCH_2$) (Scheme 8).



a) $NaBH_4$, MeOH, rt, 48 h. b) 2,2-dimethoxypropane, PTSA, 60°C, 48 h. c) TBDMSCl, imidazole, DMF, rt, 36 h. d) Ac_2O, pyridine, rt, 16 h. e) $PhCH_2Br$, NaH, THF reflux, 36 h.

SCHEME 8

In conclusion, different quinolones and a tetrahydro-4-oxoquinoline have been obtained by oxidation of **1**. Depending on the reagent, the initial addition occured either at only one of the reactive functions, namely the vinyl double bond or the enolate, or at both. New unexpected 1,2-dihydroquinolines were also synthesized in attempts to protect the diol obtained by reduction of **1**.

A first evaluation of the potential cytotoxic activity of compounds **1**, **5**, **9**, **10**, **12**, **22a**, **22c**, **22d** showed that, except for **22a**, these derivatives did not present significant antiproliferative activities to human cancer cell lines (Hela cells and HL 60 leukemia cells) *in vitro* at 10^{-5} M.

EXPERIMENTAL

All melting points were determinated on a Maquenne apparatus and are uncorrected. Elemental analyses were performed by the Microanalytical Laboratory, operated by the Bristol-Myers Squibb Analytical Department. Infrared (IR) spectra were recorded on a Perkin Elmer Model 783 infrared spectrophotometer. FAB, EI, CI MS measurements were made on a Nermag R 10-10 mass spectrometer, a quadripole instrument. NMR spectra were determinated on a Bruker AC 300 or AC 500 apparatus. Chemical shifts are expressed in ppm (δ) relative to internal tetramethylsilane. Flash columm chromatography was performed with Merck silica gel 60, 70-230 mesh ASTM.

Ethyl 3-(2-bromo-4,5-methylenedioxyphenyl)-3-oxo-2-[((3',4',5'-trimethoxyphenyl) aminomethylene]propanoate 8.

To a solution of **7** (6.29 g, 0.017 mol) in EtOH (100 ml) at 0°C 3,4,5-trimethoxyaniline (3.11 g, 0.017 mol) was added. After 12 hours at room temperature, the precipitate was filtered, washed with a small amount of EtOH and dried to give 5.33 g (62%) of **8** : IR (cm^{-1}) : 3160, 2965, 1697, 1617, 1591, 1421. MS (CI) : m/z : 509 $[MH]^+$. Elemental analysis : calcd for $C_{22}H_{22}NBrO_8$: C, 52.09; H,

4.17; N, 2.76; found : C, 51.89; H, 4.24; N, 2.76. Product **8** exists in the two E / Z forms . ^{1}H NMR (500 MHz) ($CDCl_3$) : δ 0.97 and 1.05 (t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.83 and 3.85 (s, 2xOMe), 3.88 and 3.92 (s, OMe), 4.06 (2q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.00 (s, OCH_2O), 6.41 and 6.46 (s, H-2' and H-6'), 6.72 and 6.80 (s, H-3), 6.97 (s, H-6), 8.54 (d, J=15 Hz, CH), 11.21 and 12.64 (d, J=15 Hz, NH).

Ethyl 1,4-dihydro-6,7-methylenedioxy-1-(3',4',5'-trimethoxyphenyl)-4-oxoquinoline-3-carboxylate 9.

A suspension of **8** (63 g, 0.124 mol), K_2CO_3 (17.1 g, 0.124 mol) in dry DMF (350 ml) was heated with stirring at 110°C for 5 hours. The mixture was cooled and poured into a 5% aqueous solution of AcOH. After stirring 2 hours, the product was filtered, washed with EtOH and dried to yield a yellow solid (48 g, 90%). A small amount was recrystallized from EtOH for analysis : mp>300°C; IR (cm^{-1}) : 3063, 2978, 1725, 1635, 1598. MS (CI) : m/z : 428 $[MH]^+$. Elemental analysis : calcd for $C_{22}H_{21}NO_8$: C, 61.82; H, 4.95; N, 3.28; found : C, 61.65; H, 4.73; N, 3.17. ^{1}H NMR (500 MHz) (DMSO-*d6*) : δ 1.29 (t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.82 (s, OMe), 3.85 (s, 2xOMe); 4.23 (q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.20 (s, OCH_2O), 6.49 (s, H-5 or H-8), 7.05 (s, H-2' and H-6'), 7.56 (s, H-5 or H-8), 8.33 (s, H-2). ^{13}C NMR (125 MHz) (DMSO-*d6*) : 14.18 ($OCH_2\underline{C}H_3$), 56.27 (OMe), 59.72 ($O\underline{C}H_2CH_3$), 60.08 (2xOMe), 97.43 (Ar), 102.50 (Ar), 105.31 (C-2' and C-6'), 119.65, 123.00, 135.97, 137.49, 138.18, 146.02, 146.84, 151.46, 153.59, 164.21, 171.52 (Cq).

Ethyl 2-ethenyl-6,7-methylenedioxy-1,2,3,4-tetrahydro-1-(3',4',5'-trimethoxyphenyl) -4-oxoquinoline-3-carboxylate 1 and 1,4-dihydro-6,7-methylenedioxy-3-(1-oxo-4-pentenyl)-1-(3',4',5'-trimethoxyphenyl)-4-oxoquinoline 10.

To a slurry composed of **9** (2 g, 4.68 10^{-3} mol) and CuI (1.78 g, 10 10^{-3} mol) in 100 ml of dry THF at -70°C, 14 ml of a 1.0 M solution of vinylmagnesium bromide in THF (14 10^{-3} mol) was added under N_2 atmosphere. After stirring for 1.5 hour at -70°C, another 14 ml of vinylmagnesium bromide (14 10^{-3} mol) was added and then a third amount after 45 min. The temperature was allowed to raise to -40°C and the reaction was quenched with a saturated aqueous solution of NH_4Cl. THF was removed in vacuo and the aqueous residue extracted with CH_2Cl_2 (3x60 ml). The combined organic layers were washed with brine and water, dried over Na_2SO_4, filtered and evaporated to yield a yellow residue (2.05 g). Chromatographic purification (ligroin / AcOEt 80:20 to 30:70) afforded 1.3 g (62%) of **1**, 0.59 g (24%) of **10** and 0.1 g (5%) of starting material **9**.

1 : mp 152°C (EtOH); IR (cm^{-1}) : 3445, 3080, 1699, 1633, 1593, 1508. MS (EI) : m/z : 455 $[M]^{+\cdot}$. Elemental analysis : calcd for $C_{24}H_{25}NO_8$: C, 63.29; H, 5.53; N, 3.08; found : C, 62.96; H, 5.60; N, 3.01. **1** exists in two tautomeric forms **1a** : **1b** (16 : 84) in $CDCl_3$. ^{1}H NMR (500 MHz) ($CDCl_3$) for **1a** : δ 1.22 (t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.52 (d, J=4.6 Hz, H-3), 3.85 (s, 2xOMe), 3.91 (s, OMe), 4.34 (m, $OC\underline{H}_2CH_3$), 4.75 (m, H-2), 5.25 (m, $CH{=}C\underline{H}_2$), 5.90 (m, OCH_2O), 5.91 (m, $C\underline{H}{=}CH_2$), 6.45 (s, H-2' and H-6'), 6.55 (s, H-5 or H-8), 7.36 (s, H-5 or H-8). ^{1}H NMR (500 MHz) ($CDCl_3$) for **1b** : δ 1.41 (t, J=7 Hz, $OCH_2C\underline{H}_3$), 1.53 (s, OH), 3.75 (s, 2xOMe), 3.81 (s, OMe), 4.22 (m, $OC\underline{H}_2CH_3$), 5.05 (dt, J=1.4 Hz, J=10 Hz, $CH{=}C\underline{H}_2$), 5.11 (d, J=6 Hz, H-2), 5.15 (dt, J=1.4 Hz, J=19 Hz,

CH=C$\underline{H}_2$), 5.92 (m, OCH_2O), 5.95 (m, C$\underline{H}$=CH_2), 6.41 (s, H-5 or H-8), 6.55 (s, H-2' and H-6'), 7.15 (s, H-8 or H-5).

10 : mp 248°C (EtOH); IR (cm^{-1}) : 3432, 3080, 2945, 2941, 1739, 1667, 1629, 1599, 1519. MS (CI) : m/z : 438 $[MH]^+$. Elemental analysis: calcd for $C_{24}H_{23}NO_7$: C, 65.90; H, 5.30; N, 3.20; found : C, 65.65; H, 5.27; N, 3.20. ^1H NMR (500 MHz) ($CDCl_3$): δ 2.50 (m, CH_2), 3.41 (m, CH_2), 3.85 (s, 2xOMe), 3.95 (s, OMe), 4.94 (dd, J=1.3 Hz, J=10 Hz,CH=C$\underline{H}_2$), 5.12 (dd, J=1.3 Hz, J=17 Hz, CH=C$\underline{H}_2$), 5.90 (m, C$\underline{H}$=CH_2), 6.10 (s, OCH_2O), 6.41 (s, H-8 or H-5), 6.61 (s, H-2' and H-6'), 7.85 (s, H-5 or H-8), 8.4 (s, H-2).

Reaction of the dihydroquinolone 1 with oxidative reagents.

Reaction with $KMnO_4$ at 0°C-20°C.

To a solution of **1** (100 mg, 0.22 10^{-3} mol) in acetone (3 ml) at 0°C was added dropwise $KMnO_4$ (100 mg, 0.63 10^{-3} mol) in H_2O (6 ml). The mixture was stirred for 2 hours at 0°C, and then at room temperature for 36 hours. After filtration, acetone was evaporated. The solution was extracted with CH_2Cl_2 (5x3 ml). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and evaporated to yield a yellow residue. Preparative thin layer chromatographic purification (CH_2Cl_2 / MeOH 95 : 5) afforded 71 mg (75%) of **9** and 20 mg (20%) of **5**.

Reaction with $KMnO_4$ at reflux.

The procedure was the same as described previously using compound **1** (70 mg, 0.15 10^{-3} mol), $KMnO_4$ (90 mg, 0.54 10^{-3} in H_2O (6 ml). The mixture was refluxed for 4 hours. Chromatographic purification (CH_2Cl_2 / AcOEt 70 : 30 to 50 : 50) afforded 30 mg of **11** (44%) and 26 mg of **9** (40%).

Reaction with N-methylmorpholine N-oxide (NMO) and catalytic OsO_4.

To a solution of NMO (30 mg, 0.22 10^{-3} mol) in acetone (2 ml) and H_2O (2 ml) at 0°C was added one drop of 4% aqueous solution of OsO_4 and then **1** (100 mg, 0.22 10^{-3} mol) in acetone (2 ml) and *t*-butanol (2 ml). The mixture was stirred for 36 hours at room temperature. $NaHSO_3$ (0.1 ml) was added and the solution was extracted with CH_2Cl_2 (4x3 ml). The organic extracts were combined, dried over Na_2SO_4, and concentrated in vacuo. Chromatographic purification (CH_2Cl_2 / MeOH 98 : 2 to 90 :10) afforded 30 mg (35%) of **12**, 30 mg (33%) of **11**, 33 mg (31%) of **9**.

Reaction with OsO_4.

To a solution of **1** (100 mg, 0.22 10^{-3} mol) in *t*-butanol (4 ml) and H_2O (4 ml) at 0°C was added a solution of OsO_4 (4% in H_2O, 1.25 ml). After 15 min, the mixture was allowed to reach room temperature, and then employed in this experiment following the procedure described with NMO. Chromatographic purification (CH_2Cl_2 / MeOH 98 : 2 to 90 : 10) afforded 30 mg (33%) of **12**, 29 mg (33%) of **11**, 30 mg (32%) of **9**.

Reaction with MnO_2.

To a solution of **1** (50 mg, 0.11 10^{-3} mol) in MeOH (4 ml) were added MnO_2 (50 mg, 0.57 10^{-3} mol). The mixture was stirred for 3 hours at 50°C. After filtration, MeOH was evaporated to yield 60

mg of a crude material which after chromatography (ligroin / AcOEt 90 :10 to 50 : 50) gave 36 mg (68%) of **12**.

Reaction with $NaIO_4$ / $KMnO_4$.

A solution of sodium metaperiodate (0.45 g, 2.1 10^{-3} mol) in 9.6 ml of water and $KMnO_4$ (6 mg, 0.42 10^{-3} mol), was stirred for 30 min at 25°C and treated with K_2CO_3 (30 mg, 0.243 10^{-3} mol, EtOH (3 ml) and then **1** (90 mg, 0.21 10^{-3} mol) in 4 ml of *t*-butanol, while maintaining the solution temperature at 20°C-30°C. The resulting reddish-purple suspension was stirred for 2 hours at 25°C, treated with three drops of ethylene glycol, stirred for 2 hours, acidified (pH 4) with 0.5 N aqueous HCl, and extracted with AcOEt. The combined organic extracts were washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure to yield 90 mg of crude material which upon chromatography (ligroin / AcOEt 90 :10 to 50 :50) gave 70 mg (70%) of **12**.

Reaction with metachloroperbenzoic acid (m-CPBA).

Under nitrogen, a solution of *m*-CPBA (91 mg, 0.385 10^{-3} mol) in $CHCl_3$ (2 ml) was added dropwise to a mixture of **1** (50 mg, 0.11 10^{-3} mol) and 2,6-di-*t*-butyl-4-phenol (3.6 mg, 0.038 10^{-3} mol) in 2 ml of $CHCl_3$. The mixture was stirred at room temperature for 2 hours, cooled and filtered. The filtrate was washed three times with 5 ml of 10% sodium bicarbonate aqueous solution, then dried over Na_2SO_4 and evaporated under reduced pressure to yield 50 mg of crude material which upon chromatography (ligroin / AcOEt 80 :20 to 50 : 50) gave 40 mg (75%) of **12**.

Reaction with Jones reagent and catalytic OsO_4.

To a solution of **1** (100 mg, 0.22 10^{-3} mol) in acetone (1 ml) was added a 4% wt solution of OsO_4 (20 ml, 2mol %) in water and 0.26 ml (0.69 10^{-3} mol of Cr ^{VI}) of Jones reagent. After 20 hours of stirring at room temperature, 0.1 ml of 2-propanol was added followed by 20 ml of $NaHSO_3$ and 1 ml of water. Then the mixture was stirred for 30 min. The solution was diluted with 2 ml of water and extracted with AcOEt (6x2 ml). The combined organic extracts were dried over Na_2SO_4, and concentrated in vacuo. The crude material was purified by chromatography (CH_2Cl_2 / MeOH 98 : 2 to 90 : 10) yielding 60 mg (60%) of **11**.

Ethyl 1,4-dihydro-2-ethenyl-6,7-methylenedioxy-1-(3',4',5'-trimethoxyphenyl) -4-oxoquinoline-3-carboxylate 11. mp 122°C (acetone); IR (cm^{-1}) : 3431, 2971, 2937, 2228, 1724, 1628, 1593, 1571, 1503, 1470. MS (CI) : m/z: 454 $[MH]^+$. Elemental analysis : calcd for $C_{24}H_{23}NO_8$: C, 63.57; H, 5.11; N, 3.09; found : C, 63.36; H, 4.98; N, 3.02. ^1H NMR (300 MHz) ($CDCl_3$) : δ 1.31 (t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.75 (s, 2xOMe), 3.85 (s, OMe), 4.25 (q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.35 (dd, J=1 Hz, J=11.5 Hz, $CH=C\underline{H}_2$), 5.65 (dd, J=1 Hz, 17.5 Hz, $CH=C\underline{H}_2$), 5.95 (s, OCH_2O), 6.11 (dd, J=17.5 Hz, 11.5 Hz, $C\underline{H}=CH_2$), 6.13 (s, H-5 or H-8), 6.46 (s, H-2' and H-6'), 7.65 (s, H-5 or H-8).

3-Hydroxymethyl-6,7-methylenedioxy-1,3,4,9-tetrahydro-4-(3',4',5'-trimethoxyphenyl)furo[3,4-b]quinoline-1,9-dione 5. mp>300°C; IR (cm^{-1}) : 3436, 2937, 2363, 1765, 1639, 1597, 1505. MS (CI) : m/z: 442 $[MH]^+$. Elemental analysis : calcd for $C_{22}H_{19}NO_9$

: C, 59.87; H, 4.34; N, 3.17; found : C, 59.67; H, 4.31; N, 3.02. ^{1}H NMR (500 MHz) (DMSO-*d6*) : δ 3.00 (ddd, J=2.8 Hz, 5.7 Hz, 12.7 Hz, C<u>H</u>$_2$OH), 3.61 (ddd, J=1.7 Hz, 5.7 Hz, 12.7 Hz, C<u>H</u>$_2$OH), 3.82 (s, OMe), 3.83 (s, OMe) 3.84 (s, OMe), 5.11 (t, J=5.7 Hz, OH), 5.40 (dd J=1.7 Hz, J=2.8 Hz, CH), 6.22 (m, OCH$_2$O), 6.55 (s, 5-H or 8-H), 7.02 (d, J=1 Hz, 2'-H and 6'-H), 7.66 (s, 5-H or 8-H).^{13}C (125 MHz) (DMSO-*d6*) : 57.34 (OMe), 57.46 (OMe), 59.85 (CH$_2$OH), 61.96 (OMe), 78.89 (CH), 98.67 (Ar), 103.48 (Ar), 103 99 (OCH$_2$O), 105.82 (CH), 106.85 (Ar), 107.33 (Ar), 124.03, 132.31, 139.79, 140.36, 147.40, 153.19, 154.71, 155.17, 164.56, 167.86, 171.40 (Cq).

Ethyl 2-ethenyl-3-hydroxy-6,7-methylenedioxy-1,2,3,4-tetrahydro-1-(3',4',5'-trimethoxyphenyl)-4-oxoquinoline-3-carboxylate 12. mp 206°C (EtOH); IR (cm^{-1}) : 3496, 2967, 2927, 1727, 1633, 1590, 1504. MS (CI) : m/z: 472 [MH]$^+$. Elemental analysis : calcd for C$_{24}$H$_{25}$NO$_9$: C, 61.14; H, 5.35; N, 2.97; found : C, 60.97; H, 5.42; N, 2.82. ^{1}H NMR (300 MHz) (CDCl$_3$) : δ 1.21 (t, J=7 Hz, OCH$_2$C<u>H</u>$_3$), 3.75 (s, 2xOMe), 3.81 (s, OMe), 4.22 (m, OC<u>H</u>$_2$CH$_3$), 4.31 (d, J=9 Hz, H-2), 4.35 (s, OH), 5.15 (dd, J=10 Hz, J=1.4 Hz, CH=C<u>H</u>$_2$), 5.21 (dd, J=17 Hz, J=1.4 Hz, CH=C<u>H</u>$_2$), 5.72 (ddd, J=17 Hz, J=10 Hz, J=9 Hz, C<u>H</u>=CH$_2$), 5.75 (s, H-5 or H-8), 5.85 (m, OCH$_2$O), 6.3 (s, H-2' and H-6'), 7.25 (s, H-5 or H-8).

Reaction of the dihydroquinolone 1 with N-Bromosuccinimide (NBS).

Reaction at 100°C.

A slurry of **1** (200 mg, 0.44 10^{-3} mol) in H$_2$O (4 ml) and dioxane (8 ml) was heated with NBS (82 mg, 0.44 10^{-3} mol) at 100°C for 3 hours. Dioxane was removed in vacuo and the aqueous residue extracted with CH$_2$Cl$_2$ (5x6 ml). The combined organic extracts were washed with brine and water, dried over Na$_2$SO$_4$, filtered and evaporated to yield a yellow solid (220 mg). Chromatographic purification (CH$_2$Cl$_2$ / MeOH 99 :1 to 95 : 5) afforded 120 mg (60%) of **11**.

Reaction at room temperature.

The procedure was the same as described previously using compound **1** (100 mg, 0.22 10^{-3} mol), NBS (41 mg, 0.22 10^{-3} mol), H$_2$O / dioxane at room temperature for 4 hours. The crude product (105 mg) was purified by columm chromatography purification (ligroin / AcOEt 95 : 5 to 50 : 50) gave 30 mg (30%) of **11** and 49 mg (42%) of a yellow oil **15**.

Ethyl 3-bromo-2-ethenyl-6,7-methylenedioxy-1,2,3,4-tetrahydro-1-(3',4',5' trimethoxyphenyl)-4-oxoquinoline-3-carboxylate 15. IR (cm^{-1}) : 3158, 2970, 1726, 1620, 1582, 1488. SM (CI) : m/z: 535 [MH]$^+$. Elemental analysis : calcd for C$_{24}$H$_{24}$NBrO$_8$: C, 53.94; H, 4.53; N, 2.62. found : C, 53.83; H, 4.43; N, 2.53. ^{1}H NMR (300 MHz) (CDCl$_3$) : δ 1.22 (t, J=7 Hz, OCH$_2$C<u>H</u>$_3$), 3.82 (s, 2xOMe), 3.91 (s, OMe), 4.27 (q, OC<u>H</u>$_2$CH$_3$), 4.50 (d, J=6.2 Hz, H-2), 5.22 (dd, J=1.4 Hz, J=16 Hz, CH=C<u>H</u>$_2$), 5.31 (dd, J=1.4 Hz, J=10 Hz, CH=C<u>H</u>$_2$), 5.92 (m, OCH$_2$O), 6.11 (s, H-5 or H-8), 6.14 (ddd,J=6.2 Hz, J=10 Hz, J=16 Hz, C<u>H</u>=CH$_2$), 6.62 (s, H-2' and H-6'), 7.14 (s, H-5 or H-8).

2-Ethenyl-3-methyl-6,7-methylenedioxy-1,2,3,4-tetrahydro-1-(3',4',5'-trimethoxyphenyl)-4-oxoquinoline 20.

A solution of $LiAlH_4$ (1M / THF, 0.44 10^{-3} mol, 0.44 ml) was added to a solution of **1** (0.1 g, 0.22 10^{-3} mol) in THF (5 ml) at 0°C. The mixture was heated at reflux for 5 hours. After cooling, one drop of H_2O and two drops of an aqueous solution of NaOH (15%) were added. The solvent was evaporated and the aqueous phase was extracted three times with AcOEt. The combined organic phases were washed three times with water, dried over Na_2SO_4, filtered and evaporated to yield an oil which on trituration with diisopropyl ether gave 60 mg (69%) of **20** as yellow crystals. mp 175°C; IR (cm^{-1}) : 3486, 3071, 2971, 1665, 1633, 1591, 1506. MS (CI) m/z : 398 $[MH]^+$. Elemental analysis : calcd for $C_{22}H_{23}NO_6$: C, 66.49; H, 5.83; N, 3.52; found : C, 66.14; H, 5.90; N, 3.62. ^1H NMR (500 MHz) ($CDCl_3$) : δ 1.21 (d, J=6.9 Hz, Me), 3.22 (qd, J=6.9, 5.6 Hz, H-3), 3.85 (s, 2xOMe), 3.91 (s, OMe), 4.15 (dd, J=5.6 Hz, J=8.4 Hz, H-2), 5.22 (br d, J=17.5 Hz, CH=C$\underline{H}_2$), 5.31 (br d, J=10 Hz, CH=C$\underline{H}_2$), 5.93 (m, OCH_2O), 6.04 (m, C$\underline{H}$=CH_2), 6.11 (s, H-5 or H-8), 6.63 (s, H-2' and H-6'), 7.15 (s, H-5 or H-8).

2-Ethenyl-4-hydroxy-3-hydroxymethyl-6,7-methylenedioxy-1,2,3,4-tetrahydro-1-(3',4',5'-trimethoxyphenyl)quinoline 21.

$NaBH_4$ (1.5 g, 39 10^{-3} mol) was added portionwise to a solution of **1** (1.02 g, 2.2 10^{-3} mol) in 50 ml of MeOH at 0°C . The reaction mixture was stirred for 24 hours at room temperature, cooled to 5°C and then hydrolysed with water (15 ml). The solvent was removed under vacuum and the residue extracted with AcOEt (4x10 ml). The combined organic layers were washed with brine and water, dried over Na_2SO_4 and the solvent was evaporated to yield a yellow residue (800 mg). The crude product was purified by chromatography (AcOEt / ligroin 50 : 50 to 60 : 40) yielding 430 mg (47%) of **21** as yellow crystals. **21** exists as two isomers. After recrystallization from acetone, one isomer was isolated. mp 149°C; IR (cm^{-1}) : 3484, 3329, 2965, 2633, 2881, 2835, 1587, 1505. MS FAB (thioglycerol): m/z : 416 $[MH]^+$; 415 $[M]^+$; 398 $[MH\text{-}H_2O]^+$. Elemental analysis : calcd for $C_{22}H_{25}NO_7$: C, 63.61; H, 6.07; N, 3.37; found : C, 63.67; H, 6.09; N, 3.20. ^1H NMR (500 MHz) ($CDCl_3$) : δ 1.65 (t, J=5.6 Hz, $CH_2O\underline{H}$), 2.25 (d, J=8 Hz, OH-4), 2.41 (tdd, J=6.7 Hz, J=4.8 Hz, J=4 Hz, H-3), 3.65 (br dd, J=6.7 Hz, J=5.6 Hz, C$\underline{H}_2$OH), 3.82 (s, 2xOMe), 3.85 (s, OMe), 4.29 (t, J=4.8 Hz, H-2), 4.52 (dd J=8 Hz, J=4 Hz, H-4), 5.21 (dd, J=10.5 Hz, J=1.4 Hz, CH=C$\underline{H}_2$), 5.25 (dd, J=17 Hz, J=1.4 Hz, CH=C$\underline{H}_2$), 5.85 (m, OCH_2O), 6.05 (ddd, J=17 Hz, J=10.5 Hz, J=4.8 Hz, C$\underline{H}$=CH_2), 6.43 (s, H-2' and H-6'), 6.5 (s, H-5 or H-8), 6.9 (s, H-5 or H-8). ^{13}C NMR (125 MHz) ($CDCl_3$): 49.37 (C-3), 56.16 (OMe), 60.96 (OMe), 61.17 (C-2), 62.92 (CH_2OH), 67.85 (C-4), 99.13 (Ar), 100.43 (OCH_2O), 100.78 (C-2' and C-6'), 108.42 (Ar), 115.73 (CH=$\underline{C}H_2$), 139.07 ($\underline{C}$H=CH_2), 119.00, 136.05, 142.61, 143.81, 147.90, 153.63 (Cq).

1,2-Dihydro-2-ethenyl-6,7-methylenedioxy-3-(2-methoxypropane-2-oxymethyl)-1-(3',4',5'-trimethoxyphenyl)quinoline 22a.

A slurry of **21** (70 mg, 0.17 10^{-3} mol) and PTSA (3 mg) in 2,2-dimethoxypropane (3 ml) was heated at 60°C for 48 hours. The mixture was diluted with CH_2Cl_2 (10 ml) and washed with an aqueous solution of $NaHCO_3$ (10%) (3x5 ml) and then with water. The organic layer was dried over Na_2SO_4, filtered and evaporated to yield a yellow oil which in trituration with ligroin gave 50 mg (62%) of **22a** as yellow crystals. mp 146°C; IR (cm^{-1}) : 3445, 2988, 2935, 2824, 1586, 1505, 1477. MS (CI) m/z : 470 $[MH]^+$. Elemental analysis : calcd for $C_{26}H_{31}NO_7$: C, 66.51; H, 6.66; N, 2.98; found : C,65.14; H, 6.23; N, 2.78. ^1H NMR (300MHz) ($CDCl_3$) : δ 1.39 (s, 2xMe), 3.22 (s, OMe), 3.79 (s, 2xOMe), 3.84 (s, OMe), 4.03 (s, CH_2), 4.63 (d, J=5.6 Hz, H-2), 5.04 (br d, J=10 Hz, CH=C<u>H</u>2), 5.20(br d, J=17 Hz, CH=C<u>H</u>2), 5.85 (m, OCH_2O), 5.88 (ddd, J=5.6 Hz, J=10 Hz, J=17 Hz, C<u>H</u>=CH_2), 6.40 (s, H-4), 6.50 (s, H-2' and H-6'), 6.58 (s, H-8 or H-5), 6.60 (s, H-5 or H-8).

1,2-Dihydro-2-ethenyl-6,7-methylenedioxy-3-*t*-butyldimethylsilyloxomethyl-1-(3',4',5'-trimethoxyphenyl)quinoline 22b.

Under nitrogen, a slurry composed of **21** (20 mg, 0.048 10^{-3} mol), *t*-butyldimethylsilyl chloride (TBDMSCl) (19 mg, 0.12 10^{-3} mol) and imidazole (17 mg, 0.25 10^{-3} mol) in DMF (1 ml) was stirred at room temperature for 36 hours. The mixture was diluted with ether (2 ml) and an aqueous $NaHCO_3$ saturated solution (2 ml). The aqueous layer was extracted twice with ether (2 ml). The combined extracts were washed with water, dried over Na_2SO_4, filtered and evaporated to yield a yellow oil (20 mg). Chromatographic purification (CH_2Cl_2) gave 10 mg (47%) of a yellow oil **22b** : IR (cm^{-1}) : 3400, 2922, 2840, 1592, 1522, 1483. SM (CI) : m/z: 513 $[MH]^+$. ^1H NMR (300 MHz) ($CDCl_3$) : δ 0.11 (s, Me), 0.12 (s, Me), 0.90 (s, *t*-Bu), 3.78 (s, 2xOMe), 3.84 (s, OMe), 4.23 (s, CH_2), 4.66 (d, J=5.5 Hz, H-2), 5.05 (br d, J=10 Hz, CH=C<u>H</u>2), 5.15 (br d, J=17 Hz, CH=C<u>H</u>2), 5.86 (m, OCH_2O), 5.97 (m, C<u>H</u>=CH_2), 6.41 (s, H-5 or H-8), 6.43 (s, H-4), 6.48 (s, H-2' and H-6'), 6.61 (s, H-5 or H-8).

3-Acetoxymethyl-1,2-dihydro-2-ethenyl-6,7-methylenedioxy-1-(3',4',5'-trimethoxyphenyl)quinoline 22c.

Under nitrogen, diol **21** (70 mg, 0.17 10^{-3} mol) was dissolved in dry pyridine (3 ml) and cooled to 0°C. Acetic anhydride (0.8 ml) was added dropwise. The mixture was stirred at room temperature for 16 hours. The solution was concentrated and water (3 ml) was added.The aqueous residue was extracted with CH_2Cl_2 (2x3 ml). The combined extracts were washed with a 0.5N HCl aqueous solution, followed by water and then dried over Na_2SO_4, filtered and evaporated to yield a yellow oil (65 mg). Chromatographic purification (ligroin / AcOEt 80 : 20) gave 45 mg (60%) of **22c**. IR (cm^{-1}) : 3442, 2931, 2844, 1738, 1591, 1506, 1460. MS (CI) : m/z : 440 $[MH]^+$. Elemental analysis : calcd for $C_{24}H_{25}NO_7$: C, 65.59; H, 5.73; N, 3.19; found : C, 65.29; H, 5.80; N, 2.91. ^1H NMR (300 MHz) ($CDCl_3$) : δ 1.94 (s, $COCH_3$), 3.56 (s, 2xOMe), 3.70 (s, OMe), 4.45 (d, J=6 Hz, H-2), 4.55 (s, CH_2), 4.95 (dt, J=10 Hz, J=1.4 Hz, CH=C<u>H</u>2), 5.05 (dt, J=17 Hz, J=1.4 Hz, CH=C<u>H</u>2), 5.71 (m, OCH_2O), 5.82 (ddd, J=6 Hz, J=17 Hz, J=10 Hz, C<u>H</u>=CH_2), 6.25 (s, H-4), 6.31 (s, H-2' and H-6'), 6.35 (s, H-5 or H-8), 6.46 (s, H-5 or H-8).

1,2-Dihydro-2-ethenyl-3-hydroxymethyl-6,7-methylenedioxy-1-(3',4',5'-trimethoxyphenyl)quinoline 22d.

Sodium hydride (7 mg of a 60% oil dispersion, 0.17 10^{-3} mol) was placed in the reaction flask and rinsed once with THF, then suspended in 2 ml of dry THF. After cooling to 0°C, the diol **21** (70 mg, 0.17 10^{-3} mol) in dry THF (3 ml) was added dropwise under nitrogen and stirred for 30 min at 0°C. A solution of benzyl bromide (0.05 ml, 0.4 10^{-3} mol) in dry THF (2 ml) was added. The mixture was stirred at reflux for 36 hours. A 5% aqueous solution of NaOH was added and THF was evaporated. The aqueous residue was extracted with CH_2Cl_2 (4x6 ml) and the organic layer washed with brine and water, dried over Na_2SO_4, filtered and evaporated to yield 70 mg of crude material which on chromatography (ligroin / AcOEt 80 : 20 to 50 : 50) gave a yellow oil 67 mg (55%) of **22d**. IR (cm^{-1}) : 3420, 3322, 2932, 2842, 1602, 1519, 1488, 1422. MS (CI) : m/z : 398 $[MH]^+$. ^1H NMR ($CDCl_3$) (300 MHz): δ 3.71 (s, 2xOMe), 3.75 (s, OMe), 4.25 (br s, $C\underline{H}_2OH$), 4.72 (d, J=6 Hz, H-2), 5.05 (dt, J=1.4 Hz, J=10 Hz, CH=C$\underline{H}_2$), 5.25 (dt, J=1.4 Hz, J=17 Hz, CH=C$\underline{H}_2$), 5.85 (m, OCH_2O), 6.00 (ddd, J=17 Hz, J=10 Hz, J=6 Hz, C$\underline{H}$=CH_2), 6.43 (s, H-4), 6.51 (s, H-2' and H-6'), 6.57 (s, H-5 or H-8), 6.59 (s, H-5 or H-8).

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