DESIGN AND SYNTHESIS OF 4-OXOQUINOLIN-2-YL-6-HEPTENOIC ACID DERIVATIVES AS HMG-CoA REDUCTASE INHIBITORS

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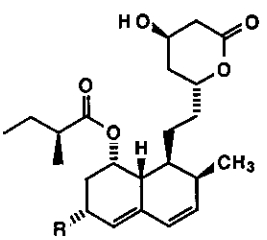
Abstract - Syntheses of two isomeric series of 4-oxoquinolin-2-yl-6-heptenoic acid derivatives **7** and **8** are described. The quinolinone portion of the molecules was constructed from the reaction of either an N-alkyl- or N-arylisatoic anhydride with an appropriate ketone enolate. The side-chain was elaborated by way of an aldol condensation using ethyl acetoacetate dianion fllowed by stereoselective ketone reduction. The N-aryl series **8** exhibited significantly greater inhibitory activity than the N-alkyl series **7**.

INTRODUCTION

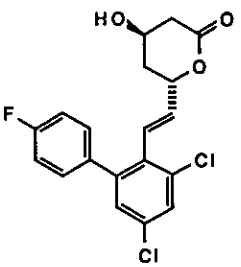
The link between coronary heart disease (CHD) and elevated levels of serum cholesterol has been clearly established.[1,2] The enormous costs in health care expenses, lost wages, and productivity has brought CHD to the forefront of medicinal research. The primary defense against CHD is dietary modification, however, when this approach fails, methods to decrease levels of endogenous cholesterol must be implemented. Pharmaceutical research has therefore concentrated on discovering hypocholesterolemic agents which will lower the circulating level of serum lipoprotein cholesterol.

An effective way to accomplish this goal is to inhibit an early step in the biosynthetic pathway leading to cholesterol. It has been shown that the fungal metabolites compactin[3] (**1**) and mevinolin[4] (**2**) exhibit potent inhibitory activity at the major rate-controlling enzyme 3-hydroxy-3-methylglutaryl coenzyme A

reductase (HMG-CoA reductase) which catalyzes the conversion of HMG-CoA to mevalonic acid. Although these natural products have many asymmetric centers (7 for compactin, 8 for mevinolin), the level of comlexity in the hexahydronaphthalene portion of the molecule is not essential to retain biological activity. The simple biphenyl analog **3** is equipotent to compactin.[5] Our group has succeeded in modifying the lower portion of the molecule with an indole moiety[6] to produce prototype **4**.



1 R = H
2 R = CH_3



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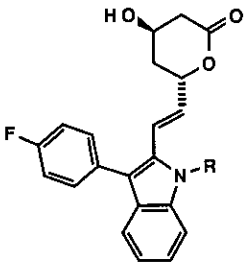

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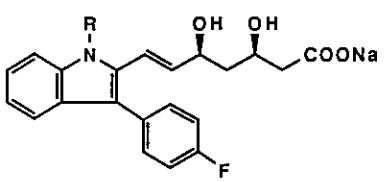
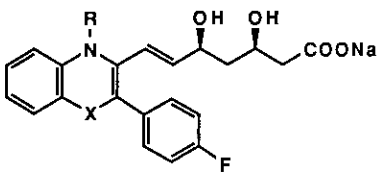
When R=CH_3, the racemate exhibits approximately one-half the inhibitory activity of compatin, however, when R=isopropyl, the activity increases markedly to 26 times that of compactin. The effect becomes even more pronounced when the lactone portion of the molecule is ring-opened to the erythro-dihydroxy acid derivative **5** . The methyl analog **5a** is equipotent to compactin whereas the isopropyl derivative **5b**, which is the subject of present clinical investigations and has been designated XU62-320, exhibits inhibitory activity 146 times that of compactin.[7]



5a R = CH_3
5b R = i-C_3H_7



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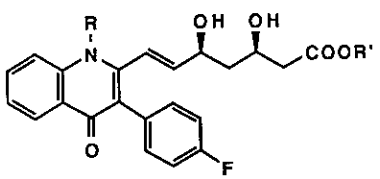
It therefore became important to investigate what effect the size of the hetero ring has on the overall activity of the molecule. In this paper we will discuss the expansion of the indole ring by one carbon atom to produce a quinoline system. Keeping the relationship of the alkyl, 4-fluorophenyl, and side-chain constant dictates that the additional carbon can only be included as shown in structure **6**. Insertion of a methylene ($X=CH_2$) in the ring would form a 1,4-dihydroquinoline system and render the nitrogen enamine-like therefore limiting stability and manageability of intermediates as well as the final products. However, inclusion of a carbonyl function (X= C=O) at the 4-position, thus forming a 4-quinolinone system, would apparently satisfy these requirements.



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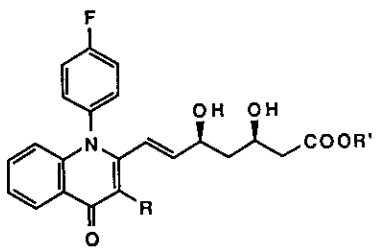

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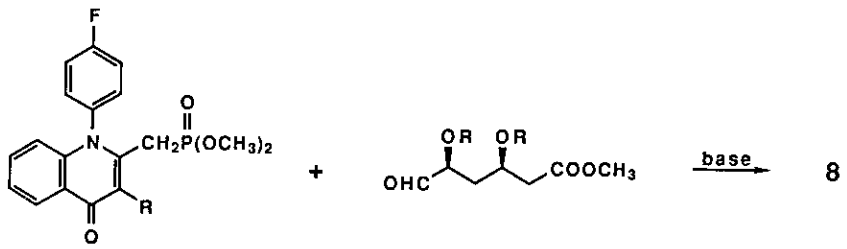
a, R = CH_3
b, R = i-C_3H_7

Upon closer examination of structure **6** one also realizes that the arrangement of the peripheral functionalities can be reversed while still keeping them in the proper relationship. That is, the 4-fluorophenyl can take the place of the alkyl group on the nitrogen while the alkyl, in turn, can be placed in the 3-position of the quinoline ring. Consequently, our goal is to synthesize the four target compounds **7a**, **7b** and **8a**, **8b**.

SYNTHESIS

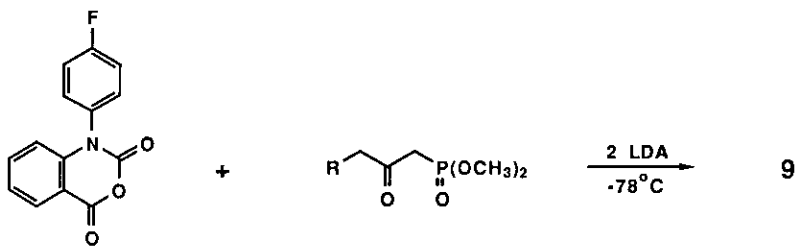
Retrosynthetically, the construction of these compounds can be approached in a convergent manner and would involve a Horner-Emmons reaction of a phosphonate such as **9** (for the N-aryl series) with the aldehydic side-chain synthon **10**. Since **10** is available in both racemic[8,9] and chiral[10] form, both achiral and optically active products can conceivably be prepared in relatively few steps.



9a R = CH_3
9b R = i-C_3H_7

10
R = t-$C_4H_9SiPh_2$

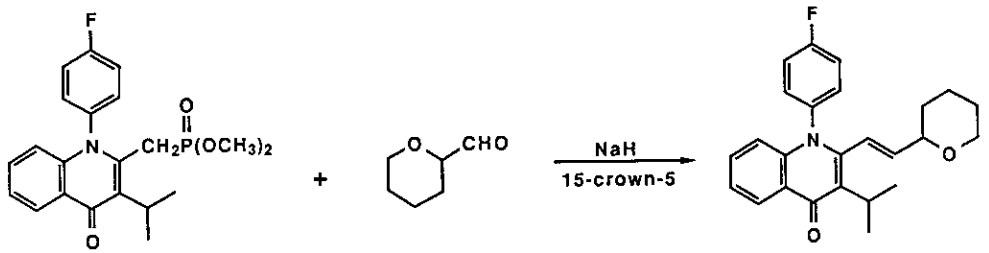
Phosphonates **9a** and **9b** are obtainable in a single step from the reaction of N-(4-fluorophenyl)isatoic anhydride[11] (**11**) with the dianion of the corresponding β-ketophosphonate[12] (**12**). In this manner, **9a** and **9b** are obtained in 40% and 50% yields, respectively.



11 **12**

The Horner-Emmons reaction of **9** with **10** unfortunately failed to produce any coupled olefinic product under many conditions.[13] Varying the temperature, time, solvent, base, and additives produces the same results. In nearly every case the phosphonate is recovered unchanged whereas the aldehyde suffers complete degradation. Analogous results are obtained for the isomeric N-alkyl-3-aryl series.

In order to test the viability of the phosphonate anion, the reaction of **9b** with a simpler α-oxygenated aldehyde (e.g. **13**) was performed and indeed the expected product **14** was obtained in 46% yield.

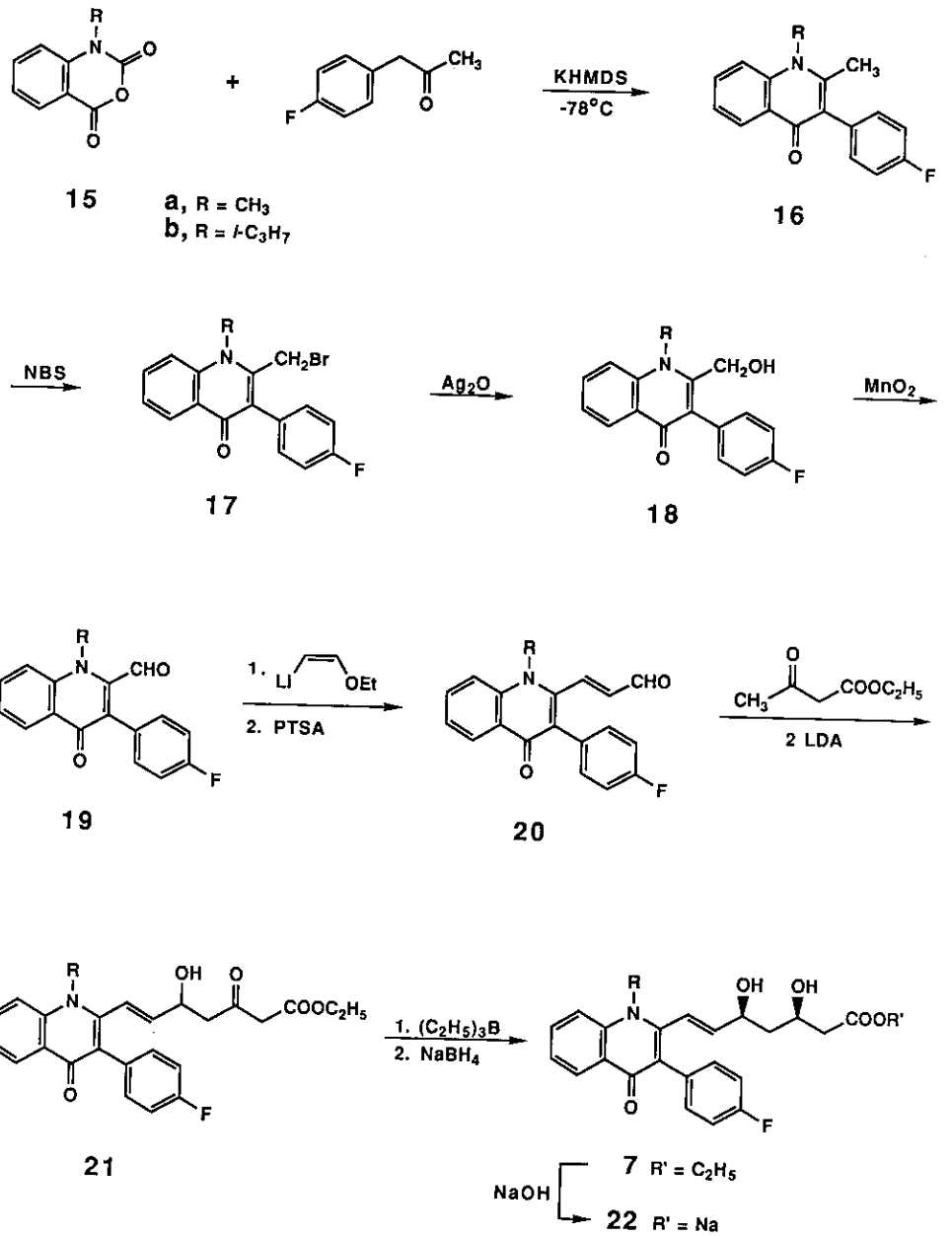


9b **13** **14**

The failure of the convergent approach to produce any product forced us to adopt a linear strategy for the completion of the syntheses of compounds **7** and **8** (see Schemes 1 and 2). Since 1,2-dialkyl-3-aryl-4-quinolinones can be prepared in a single step from the reaction of an N-alkylisatoic anhydride with the thermodynamic potassium enolate of phenylacetone,[14] extension of this methodology to our system would allow us to gain entrance to the appropriately functionalized 4-quinolinones required for the synthesis of **7**. Thus, when either N-methylisatoic anhydride (**15a**) or N-isopropylisatoic anhydride (**15b**) is allowed to react with the potassium enolate of 4-fluorophenylactone at -78°C, a near instantaneous reaction occurs to give an acyclic intermediate which spontaneously undergoes a dehydrative cyclization upon work-up to afford **16a** or **16b** in 83% yield.

A benzylic-type bromination with NBS furnishes **17** in 81% yield. Aqueous hydrolysis of **17** in the presence of silver (I) oxide furnishes the rather insoluble 2-hydroxymethyl derivative **18**. Direct oxidation with manganese dioxide affords aldehyde **19a** in 67% overall yield from **17a** and **19b** in 81% overall yield from **17b**. The aldehyde, which is essentially pure, is used in the following step without purification due to its propensity to hydrate especially when exposed to silica gel. Homologation to the α,β-unsaturated aldehyde **20** is accomplished in moderate yield with cis-2-ethoxyvinyllithium[15] at -90°C.

Elaboration of the remainder of the side-chain is effected by means of an aldol condensation of **20** with the lithium dienolate of ethyl acetoacetate to give **21** followed by a stereoselective chelation-controlled reduction[16] of the β-ketoester function to the desired erythro-β,δ-dihydroxyester **22**. Reductions using this


KHMDS
-78°C
15
a, R = CH3
b, R = i-C3H7
16
NBS
17
Ag2O
18
MnO2
19
1. LiOEt
2. PTSA
20
2 LDA
21
1. (C2H5)3B
2. NaBH4
7 R' = C2H5
NaOH
22 R' = Na

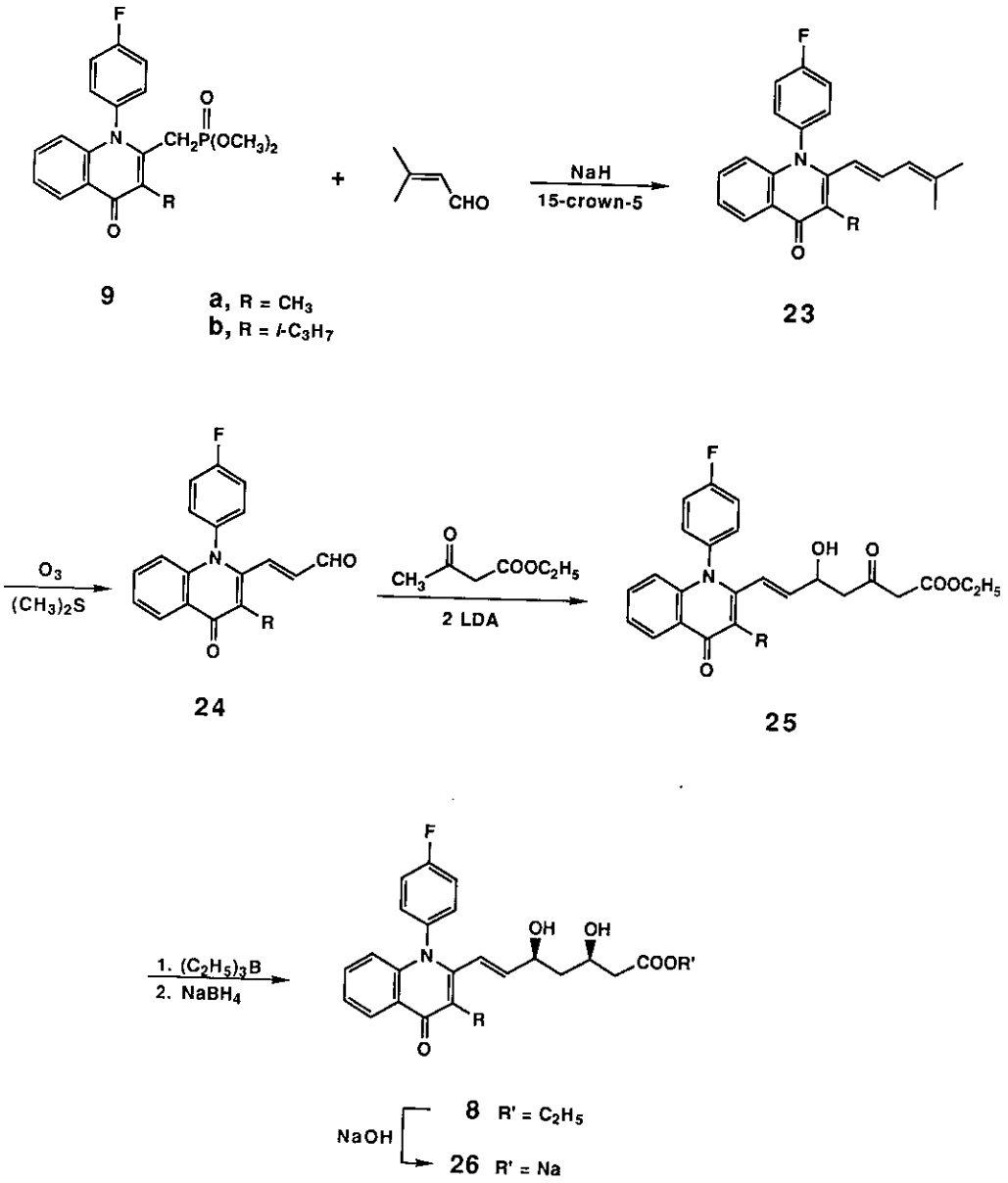
Scheme 1

methodology routinely afford between 85:15 to 90:10 ratio of erythro:threo diols. In this manner **7a** is obtained in 66% overall yield from **20a** and **7b** in 36% yield from **20b**.

In order to prepare the isomeric series **8** one can envision a similar synthetic stragegy to prepare the requisite 1-aryl-2,3-dialkyl-4-quinolinone by using **11** and an unsymmetrical dialkyl ketone enolate. A potential drawback to this route is that bromination of the 2-methyl group of the resultant quinolinone is not likely to occur regioselectively in the presence of the 3-alkyl substituent. However, since we had quantities of phosphonates **9a** and **9b** on hand we felt that they could be utilized to our advantage to synthesize the target compounds **8** in a relatively expeditious fashion. Conceptually, this could be accomplished by converting the phosphonate to a 1,3-diene by way of a Wittig-type reaction, then selective ozonolysis of the terminal olefin would give the α,β-unsaturated aldehyde.

Ideally, the terminal olefin should be dialkylated in order to increase its electron density with respect to the internal olefin therefore biasing it favorably towards selective ozonolysis. Consequently, a likely aldehyde to choose in the phosphonate coupling is 3,3-dimethylacrolein. The Wittig reaction between **9** and 3,3-dimethylacrolein is performed under modified Wadsworth-Emmons conditions using sodium hydride to generate the phosphonyl-stabilized anion and 15-crown-5 as a rate enhancer.[17] The desired dienes are formed in good yields with **23a** being isolated in 60% yield and **23b** in 70% yield (Scheme 2).

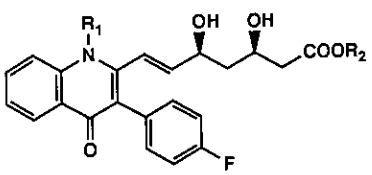
Ozonolysis of **23** is performed in methylene chloride at -78°C until exactly the point where starting material is consumed. Reaction times continuing past this point result in severe degradation of the product. Still, the products **24a** and **24b** are formed in only 25% and 34% yields, respectively. Completion of the synthesis parallels that of Scheme 1 to afford the desired erythro-β,δ-dihydroxyesters **8a** in 10% overall yield from **24a** and **8b** in 53% yield from **24b**.


F
O
N
CH2P(OCH3)2
R
O
9
a, R = CH3
b, R = i-C3H7
+
CHO
NaH
15-crown-5
F
N
R
O
23
O3
(CH3)2S
F
N
CHO
R
O
24
O
CH3
COOC2H5
2 LDA
F
OH
O
N
COOC2H5
R
O
25
1. (C2H5)3B
2. NaBH4
F
OH
OH
N
COOR'
R
O
NaOH
8 R' = C2H5
26 R' = Na

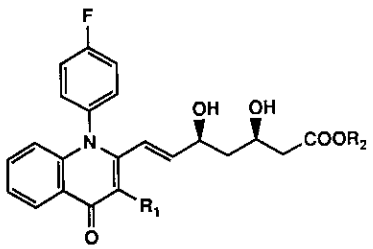
Scheme 2

PHARMACOLOGICAL RESULTS

The compounds were tested in a rat liver microsomal preparation as inhibitors of HMG-CoA reductase as described by Ackerman, et al.[18] and the results are listed below.



7



8

R_1	R_2	IC_{50} (μM)
CH_3	C_2H_5	>10
CH_3	Na	>10
CH_3	lactone	>10
$i\text{-}C_3H_7$	C_2H_5	9.070
$i\text{-}C_3H_7$	Na	3.754

R_1	R_2	IC_{50} (μM)
CH_3	C_2H_5	>10
CH_3	Na	9.1*
$i\text{-}C_3H_7$	C_2H_5	0.104
$i\text{-}C_3H_7$	Na	0.049

* *in situ* saponification of **8a**

		IC_{50} (μM)
Compactin	(lactone)	1.01
	(Na salt)	0.154
Mevinolin	(lactone)	0.352
	(Na salt)	0.068
XU 62-320		0.0069

Compounds of structural type **7** when substituted with a methyl group at R_1 are inactive either as its ester, lactone, or sodium salt. When the methyl is replaced with an isopropyl group, one begins to observe inhibitory activity to the extent of one-ninth that of compactin. Conversion of the ester to a sodium salt (**22b**) increases the activity to approximately one-fourth that of compactin.

In the N-aryl series **8**, the 3-methyl analog **8a** exhibits no activity but its sodium salt begins to show some response. A dramatic increase in activity is observed when the methyl is changed to an isopropyl group. The ester **8b** is nearly 10x as active as compactin and its sodium salt (**26b**) increases the activity to nearly 21x that of compactin.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457, or Analect FX-6200 spectophotometers. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded on Jeol FX-90-Q and Jeol JNM-FX200 spectrometers using Me_4Si as an internal reference. Chemical shifts are quoted in parts per million (s=singlet, d=doublet, t=triplet, q=quartet, m=mulitplet).

Dimethyl [1-(4-fluorophenyl)-1,4-dihydro-3-methyl-4-oxoquinolin-2-yl]methylphosphonate (**9a**). To a solution of 4.0 g (0.04 mol) of diisopropylamine in 100 ml of dry tetrahydofuran at 0°C (under a blanket of nitrogen) was added 2.56 g (0.04 mol) of n-butyllithium (as a 1.6 M solution in hexane). After sitrring at 0°C for 5 min, a solution of 3.6 g (0.02 mol) of **12a**[12] in 25 ml of tetrahydrofuran was added dropwise. The solution was stirred at 0°C for 1 h then was cooled to -78°C after which a solution of 2.57 g (0.01 mol) of **11**[11] in 35 ml of tetrahydrofuran was added slowly. Stirring was continued at -78°C for 10 min then the reaction mixture was quenched with saturated ammonium chloride. The mixture was extracted with methyl t-butyl ether (1x) and methylene chloride (2x). The organic phases were combined and dried over sodium sulfate. Removal of the solvent under reduced pressure furnished an oil which was dissolved in 75 ml of toluene. The solution was refluxed for 3 h, then the solvent was removed under reduced pressure. The resulting crude material was chromatographed on a Waters Prep-500 apparatus using 5% acetone/ethyl acetate to elute the product, 1.5 g (40%) of **9a**. An analytical sample was crystallized from ethyl acetate, mp 160-162°C; ir ($CHCl_3$): 1601, 1232, 1055 cm^{-1}; ^1H-nmr ($CDCl_3$): δ 8.40 (dd, J=6.75 and 3 Hz, 1H), 7.51-7.13 (m, 6H), 6.53 (m, 1H), 3.61 (d, J=11 Hz, 6H), 3.17 (d, J=22 Hz, 2H), 2.30 (d, J=2.5 Hz, 3H). Anal. Calcd for $C_{19}H_{19}NO_4FP$: C, 60.80; H, 5.10; N, 3.73. Found: C, 60.40; H, 5.00; N, 3.60.

Dimethyl [1-(4-fluorophenyl)-1,4-dihydro-3-(1-methylethyl)-4-oxoquinolin-2-yl]-methylphosphonate (**9b**). The reaction was performed in the same manner and on the same scale as that of **9a**. Thus, 2.57 g (0.01 mol) of **11**[11] and 4.2 g (0.02 mol) of **12b**[12] produced an intermediate which was dissolved in 125 ml of toluene and refluxed for 18 h . The solvent was removed under reduced pressure and the residue was chromatographed on a Waters Prep-500 apparatus using ethyl acetate to elute the product, 1.8 g (45%) of **9b**. Trituration with cold ethyl acetate produced an analytical sample, mp 143-145°C; ir ($CHCl_3$): 1598, 1238, 1037 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 8.40 (dd, J=6.75 and 3 Hz, 1H), 7.52 - 7.13 (m, 6H), 6.49 (m, 1H), 3.65 (d, J=11 Hz, 6H), 3.21 (d, J=22 Hz, 2H), 3.06 (m, 1H), 1.54 (d, J=7 Hz, 6H). Anal. Calcd for $C_{21}H_{23}NO_4FP$: C, 62.53; H, 5.75; N, 3.47. Found: C, 62.11; H, 5.89; N, 3.08.

1-(4-Fluorophenyl)-3-(1-methylethyl)-2-[2-(tetrahydro-2H-pyran-2-yl)ethenyl]-4(1H)-quinolinone (**14**). To a suspension of 18 mg of sodium hydride (50% in mineral oil, pentane washed) and 2 mg of 15-crown-5 in 2 ml of tetrahydrofuran at 0°C was added dropwise a solution of 150 mg (0.00037 mol) of **9b** and 45 mg (0.00039 mol) of **13** in 1 ml tetrahydrofuran. The mixture was allowed to warm to room temperature and stirred there for 3 h. The mixture was poured into water and was extracted with methyl t-butyl ether (1x) and methylene chloride (2x). The organic solutions were combined and the solvent was removed under reduced pressure. The resulting solid was purified by hplc (30% acetonitrile/methylene chloride) to give 62 mg (46%) of **14**, mp 224-225°C; ir ($CHCl_3$): 1617, 1593, 1509 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 8.48 (dd, J=6.75 and 3 Hz, 1H), 7.44-7.10 (m, 6H), 6.63 (d, J=7.5 Hz, 1H), 5.97 (dd, J=15 and 2.5 Hz, 1H), 5.62 (dd, J=17.5 and 5 Hz, 1H), 3.93 (m, 1H), 3.74 (m, 1H), 3.39 (m, 1H), 3.18 (m, 1H), 1.78 (m, broad, 2H), 1.47 (m, 3H), 1.44 (d, J=7 Hz, 6H), 1.02 (m, 1H); ms Calcd for $C_{25}H_{26}NO_2F$: MH, 392.2026. Found: MH^+, 392.2019.

1,2-Dimethyl-3-(4-fluorophenyl)-4(1H)-quinolinone (**16a**). To a solution of 16 g (0.08 mol) of potassium hexamethyldisilazide (as a 0.665 M solution in toluene)[19] in 200 ml of dry tetrahydrofuran (under nitrogen) at -78°C was added dropwise a solution of 12.4 g (0.08 mol) of 4-fluorophenylacetone in 80 ml of tetrahydrofuran. After stirring at -78°C for 1 h, a solution of 7.2 g (0.04 mol)

of **15a** in 200 ml of tetrahydrofuran was added slowly. The resulting yellow solution was stirred at -78°C for 10 min then was quenched with saturated ammonium chloride solution. The mixture was extracted with methyl t-butyl ether (1x) and methylene chloride (2x). The organic solutions were combined and dried over sodium sulfate. The solvent was removed under reduced pressure and ethyl acetate was added to the residue to afford 9.0 g (83%) of **16a** , mp 238-241°C; ir ($CHCl_3$): 1605, 1493, 1313 cm^{-1}; ^1H-nmr ($CDCl_3$): δ 8.47 (dd, J=8 and 2 Hz, 1H), 7.78-6.94 (m, 7H), 3.82 (s, 3H), 2.37 (s, 3H). Anal. Calcd for $C_{17}H_{14}NOF$: C, 76.39; H, 5.28; N, 5.24. Found: C, 76.34; H, 5.50; N, 5.26.

3-(4-Fluorophenyl)-2-methyl-1-(1-methylethyl)-4(1H)quinolinone (**16b**). The reaction of **15b**[20] with 4-fluorophenylacetone was performed according to the procedure described for the preparation of **16a**. The product **16b** was isolated in 83% yield. An analytical sample was crystallized from methyl t-butyl ether, mp 175-178°C; ir ($CHCl_3$): 1588, 1509, 1242 cm^{-1}; ^1H-nmr ($CDCl_3$): δ 8.46 (dd, J=8 and 2 Hz, 1H), 7.83-6.95 (m, 7H), 5.04 (m, 1H), 2.39 (s, 3H), 1.77 (d, J=7 Hz, 6H). Anal. Calcd for $C_{19}H_{18}NOF$: C, 77.27; H, 6.14; N, 4.74; F, 6.43. Found: C, 76.93; H, 6.25; N, 4.61; F, 6.56.

2-Bromomethyl-3-(4-fluorophenyl)-1-methyl-4(1H)-quinolinone (**17a**). A mixture of 6.0 g (0.022 mol) of **16a** and 4.0 g (0.022 mol) of N-bromosuccinimide in 50 ml of carbon tetrachloride was stirred at 60°C for 18 h. The solvent was removed under reduced pressure and the residual solid was chromatographed on a Waters Prep-500 apparatus using 10% ethyl acetate/methylene chloride to elute the product, 6.3 g (81%) of **17a** . An analytical sample was crystallized from methylene chloride/methyl t-butyl ether, mp 210-213°C; ir ($CHCl_3$): 1598, 1503, 1321, 1229 cm^{-1}; ^1H-nmr ($CDCl_3$): δ 8.43 (dd, J=8 and 2 Hz, 1H), 7.85-6.96 (m, 7H), 4.38 (s, 2H), 3.93 (s, 3H). Anal. Calcd for $C_{17}H_{13}NOBrF$: C, 58.98; H, 3.79, N, 4.05; Br, 23.08. Found: C, 59.02; H, 3.89; N, 3.89; Br, 23.20.

2-Bromomethyl-3-(4-fluorophenyl)-1-(1-methylethyl)-4(1H)-quinolinone (**17b**). Bromination of **16b** was performed according to the procedure described for the preparation of **17a**. The product **17b** was isolated in 81% yield. An analytical sample was crystallized from methyl t-butyl ether, mp 183-186°C; ir ($CHCl_3$): 1593, 1398, 1297, 1234 cm^{-1}; ^1H-nmr ($CDCl_3$): δ 8.47 (dd, J=8 and 2 Hz, 1H),

7.95-7.01 (m, 7H), 5.21 (m, 1H), 4.37 (s, 2H), 1.90 (d, J=7 Hz, 6H). Anal. Calcd for $C_{19}H_{17}NOBrF$: C, 60.98; H, 4.58; N, 3.74; Br, 21.35. Found: C, 60.71; H, 4.35; N, 3.50; Br, 21.44.

3-(4-Fluorophenyl)-2-hydroxymethyl-1-methyl-4(1H)-quinolinone (**18a**). A mixture of 7.0 g (0.02 mol) of **17a** and 17.5 g (0.075 mol) of silver (I) oxide in 300 ml of 30% aqueous tetrahydrofuran was stirred at 75°C for 24 h. While hot, the inorganic salts were filtered from the mixture and washed thoroughly with methylene chloride. Methanol was added to the filtrate to obtain a solution which was then treated with decolorizing carbon. Removal of the solvent under reduced pressure furnished 6.1 g of **18a** which was used without further purification in the next step. An analytical sample was crystallized from methanol/ethyl acetate, mp 269-272°C; ir (KBr): 3420, 1599, 1570 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 8.39 (dd, J=8 and 2 Hz, 1H), 7.81-7.01 (m, 7H), 4.60 (s, 2H), 4.08 (s, 3H); ms m/z 283 (M^+).

3-(4-Fluorophenyl)-2-hydroxymethyl-1-(1-methylethyl)-4(1H)-quinolinone (**18b**). A mixture of 4.5 g (0.012 mol) of **17b** and 11.0 g (0.062 mol) of silver (I) oxide was reacted according to the procedure described for the preparation of **18a** to give 4.5 g of **18b**. This was carried to the next step without further purification. ir (KBr): 3370, 1605 cm^{-1}; ^{1}H-nmr ($CDCl_3$ + DMSO): δ 8.35 (dd, J=8 and 2 Hz, 1H), 8.00-6.92 (m, 7H), 5.46 (t, J=8 Hz, 1H), 4.60 (m, 1H), 4.50 (s, broad, 2H), 1.83 (d, J=7 Hz, 6H).

1,4-Dihydro-3-(4-fluorophenyl)-1-methyl-4-oxo-2-quinolinecarboxaldehyde (**19a**). A mixture of 6.0 g (0.02 mol) of **18a** and 25 g of manganese dioxide in 500 ml of methylene chloride was stirred at room temperature for 48 h. The excess manganese dioxide was filtered from the mixture and was thoroughly washed with methylene chloride. Removal of the solvent under reduced pressure furnished 4.9 g of a solid which was crystallized from methylene chloride/methyl t-butyl ether to give 4.1 g (67% from **17a**) of **19a**, mp 215-218°C; ir ($CHCl_3$): 1702, 1601 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 9.70 (s, 1H), 8.45 (dd, J=8 and 2 Hz, 1H), 7.88-7.01 (m, 7H), 3.95 (s, 3H). Anal. Calcd for $C_{17}H_{12}NO_2F$: C, 72.59; H, 4.30; N, 4.98; F, 6.75. Found: C, 72.24; H, 4.27; N, 4.89; F, 6.94.

1,4-Dihydro-3-(4-fluorophenyl)-1-(1-methylethyl)-4-oxo-2-quinolinecarboxaldehyde (**19b**). A mixture of 4.5 g (0.015 mol) of **18b** and 16 g of manganese dioxide was stirred at room temperature for 48 h. The excess manganese dioxide was filtered from the mixture and the solvent was removed under reduced pressure to give 3.0 g (81% from **17b**) of **19b** as a foam. This was used directly in the following reaction. ir ($CHCl_3$): 1710, 1625, 1600 cm^{-1}; ^1H-nmr ($CDCl_3$): δ 9.78 (s, 1H), 8.40 (dd, J=8 and 2 Hz, 1H), 7.86-7.01 (m, 7H), 4.85 (m, 1H), 1.73 (d, J=7 Hz, 6H); ms m/z 309 (M^+).

3-[3-(4-Fluorophenyl)-1,4-dihydro-1-methyl-4-oxoquinolin-2-yl]-(E)-2-propenal (**20a**). To a solution of 12.0 g (0.033 mol) of cis-1-ethoxy-2-tri-n-butylstannylethylene[15] in 200 ml of tetrahydrofuran at -78°C, under nitrogen, was added dropwise 2.1 g (0.032 mol) of n-butyllithium (as a 1.6 M solution in hexane). After stirring at -78°C for 1 hr a solution of 3.0 g (0.01 mol) of **19a** in 125 ml of tetrahydrofuran was added dropwise then the mixture was stirred at -90°C for 48 h. The reaction mixture was quenched with water and was extracted with methyl t-butyl ether (1x) and methylene chloride (1x). The organic phases were combined and dried over sodium sulfate. After removal of the solvent under reduced pressure, the residual oil was partitioned between hexane and acetonitrile in order to remove any organotin contaminants. The acetonitrile phase was evaporated under reduced pressure and the residue was dissolved in 200 ml of 5% aqueous tetrahydrofuran. To this solution was added 4.5 g of p-toluenesulfonic acid and the mixture was stirred at room temperature for 5 h. The solution was poured into 10% aqueous sodium bicarbonate solution and was extracted with methyl t-butyl ether (1x) and methylene chloride (1x). The organic phases were combined and dried over sodium sulfate. Removal of the solvent under reduced pressure furnished an oil which was purified by flash chromatography using 2% methanol/methylene chloride to elute the product 1.8 g (55%) of **20a** as a solid, mp 159-162°C. This was used directly in the following step without further purification. ir ($CHCl_3$): 1696, 1596 cm^{-1}; ^1H-nmr ($CDCl_3$): δ 9.55 (d, J=7 Hz, 1H), 8.44 (dd, J=8 and 2 Hz, 1H), 7.83-6.91 (m, 8H), 6.19 (dd, J=16 and 7 Hz, 1H), 3.82 (s, 3H); ms m/z 307 (M^+).

3-[3-(4-Fluorophenyl)-1,4-dihydro-1-(1-methylethyl)-4-oxoquinolin-2-yl]-(E)-2-propenal (**20b**). This compound was prepared according to the procedure described

for **20a** using 3.0 g of **19b**, 10.0 g of cis-1-ethoxy-2-tri-n-butylstannylethylene, and 1.8 g of n-butyllithium. In this manner, 1.9 g (59%) of **20b** was isolated as a foam and was used in the following step. ^{1}H-nmr ($CDCl_3$): δ 9.56 (d, J=7 Hz, 1H), 8.45 (dd, J=8 and 2 Hz, 1H), 7.85-6.92 (m, 8H), 6.12 (dd, J=16 and 7 Hz, 1H), 4.70 (m, 1H), 1.76 (d, J=7 Hz, 6H).

7-[3-(4-Fluorophenyl)-1,4-dihydro-1-methyl-4-oxoquinolin-2-yl]-5-hydroxy-3-oxo-(E)-6-heptenoic acid ethyl ester (**21a**). To a solution of 3.4 g (0.033 mol) of diisopropylamine in 100 ml of tetrahydrofuran at 0°C (under a blanket of nitrogen) was added 2.2 g (0.033 mol) of n-butyllithium (as a 1.6 M solution in hexane). After stirring at 0°C for 5 min, a solution of 2.2 g (0.016 mol) of ethyl acetoacetate in 25 ml of tetrahydrofuran was added dropwise. The solution was stirred at 0°C for 1 h then was cooled to -20°C after which a solution of 2.2 g (0.007 mol) of **20a** in 50 ml of tetrahydrofuran was added dropwise. Stirring was continued at -20°C for 4 h then the reaction mixture was quenched with saturated ammonium chloride solution. The mixture was extracted into methyl t-butyl ether (1x) and methylene chloride (2x). The organic phases were combined and dried over sodium sulfate. The solvent was removed under reduced pressure to give **21a** which was used in the next step without any further purification.

7-[3-(4-Fluorophenyl)-1,4-dihydro-1-(1-methylethyl)-4-oxoquinolin-2-yl]-5-hydroxy-3-oxo-(E)-6-heptenoic acid ethyl ester (**21b**). This compound was prepared according to the procedure described for **21a** using 1.8 g of **20b**, 1.8 g of ethyl acetoacetate, 2.8 g of diisopropylamine, and 1.8 g of n-butyllithium. The crude product was used in the next step without purification.

7-[3-(4-Fluorophenyl)-1,4-dihydro-1-methyl-4-oxoquinolin-2-yl]-(R*,S*)-3,5-dihydroxy-(E)-6-heptenoic acid ethyl ester (**7a**). To a solution of 4.9 g (0.011 mol) of **21a** in 200 ml of tetrahydrofuran was added dropwise 12.0 ml of a 1 M solution of triethylborane in tetrahydrofuran. After stirring at room temperature for 2 h , the yellowish solution was cooled to -78°C then 0.43 g (0.012 mol) of sodium borohydride was added in one portion. The mixture was stirred at -78°C for 24 h then was carefully quenched with saturated ammonium chloride. The mixture was extracted with methyl t-butyl ether (1x) and methylene chloride (1x). The organic phases were combined and dried over sodium sulfate. The solvent was removed under reduced pressure and 100 ml of methanol was added

to the residual oil. After refluxing for 5 min, the methanol was removed under reduced pressured and the residue was flash chromatographed using a gradient system of 2% methanol/methylene chloride → 10% methanol/methylene chloride to give 2.1 g of **7a** (66% overall from **20a**) as a foam; ir ($CHCl_3$): 3391, 1730, 1591 cm^{-1}; ^1H-nmr ($CDCl_3$): δ 8.43 (dd, J=8 and 2 Hz, 1H), 7.74-6.88 (m, 7H), 6.40 (d, J=17.5 Hz, 1H), 5.51 (dd, J=17.5 and 5 Hz, 1H), 4.32 (m, 1H), 4.16 (q, J=7.5 Hz, 2H), 4.06 (m, broad, 3H), 3.79 (s, 3H), 2.38 (m, 2H), 1.30-1.10 (m, 2H), 1.27 (t, J=7.5 Hz, 3H); ms Calcd for $C_{25}H_{26}NO_5F$: M, 439.1793. Found: M^+, 439.1818.

7-[3-(4-Fluorophenyl)-1,4-dihydro-1-(1-methylethyl)-4-oxoquinolin-2-yl]-(R*,S*)-3,5-dihydroxy-(E)-6-heptenoic acid ethyl ester (**7b**). This compound was prepared according to the procedure described for **7a** using 5.1 g of crude **21b**, 11.0 ml of triethylborane solution, and 0.42 g of sodium borohydride. The crude product was flash chromatographed using 5% methanol/methylene chloride to give pure **7b**, 0.898 g (36% overall from **20b**) as a foam; ir ($CHCl_3$): 3471, 1720, 1598 cm^{-1}; ^1H-nmr ($CDCl_3$): δ 8.46 (dd, J=8 and 2 Hz, 1H), 7.80 (d, J=7.5 Hz, 1H), 7.60 (m, 1H), 7.38-6.92 (m, 5H), 6.45 (d, broadened, J=17.5 Hz, 1H), 5.50 (dd, J=17.5 and 5 Hz, 1H), 5.13 (m, 1H), 4.33 (m, 1H), 4.18 (q, J=7.5 Hz, 2H), 4.08 (m, 1H), 3.87 (s, broad, 1H), 3.71 (s, broad, 1H), 2.37 (d, 2H), 1.75 (d, J=7 Hz, 6H), 1.28 (t, J=7.5 Hz, 3H), 1.22-0.86 (m, 2H); ms calcd for $C_{27}H_{30}NO_5F$: M, 467.2098. Found: M^+, 467.2054.

7-[3-(4-Fluorophenyl)-1,4-dihydro-1-methyl-4-oxoquinolin-2-yl]-(R*,S*)-3,5-dihydroxy-(E)-6-heptenoic acid sodium salt (**22a**). To a solution of 0.78 g (0.0018 mol) of **7a** in 20 ml of ethanol was added 1.77 ml of 1.0 N sodium hydroxide. After stirring at 60°C for 3 h, the ethanol was removed under reduced pressure. Water (20 ml) was added to the residue and the mixtue was washed with methyl t-butyl ether. The aqueous phase was lyopholyzed to produce 0.695 g (90%) of **22a** as an amorphous solid; ir (KBr): 3423, 1575 cm^{-1}; ^1H-nmr (D_2O): δ 7.95 (dd, J=8 and 2 Hz, 1H), 7.68-6.90 (m, 7H), 6.23 (d, J=17.5 Hz, 1H), 5.43 (dd, J=17.5 and 5 Hz, 1H), 4.65 (m, 2H), 4.15 (m, 1H), 3.58 (s, 3H), 3.38 (m, 1H), 2.10 (m, 2H), 1.47-1.00 (m, 2H).

7-[3-(4-Fluorophenyl)-1,4-dihydro-1-(1-methylethyl)-4-oxoquinolin-2-yl]-(R*,S*)-3,5-dihydroxy-(E)-6-heptenoic acid sodium salt (**22b**). This compound was prepared according to the procedure described for **22a** using 0.84 g of **7b** and 1.80 ml of

1.0 N sodium hydroxide to give 0.81 g (97%) of **22b**, mp 105-110°C; ir (KBr): 3429, 1595 cm^{-1}; ^{1}H-nmr (D_2O): δ 8.06 (dd, J=8 and 2 Hz, 1H), 7.89 (d, J=7.5 Hz, 1H), 7.55 (t, J=7.5 Hz, 1H), 7.36 (t, J=7.5 Hz, 1H), 7.15-6.85 (m, 4H), 6.35 (d, J=17.5 Hz, 1H), 5.42 (dd, J=17.5 and 5 Hz, 1H), 5.07 (m, 1H), 4.63 (m, 2H), 4.09 (m, 1H), 3.38 (m, 1H), 2.10 (m, 2H), 1.47 (dd, 6H), 1.42-0.95 (m, 2H).

1-(4-Fluorophenyl)-3-methyl-2-(4-methyl-1,3-pentadienyl)-4(1H)-quinolinone (**23a**). To a suspension of 0.14 g (0.003 mol) of sodium hydride (50% in mineral oil) and 0.07 g of 15-crown-5 in 15 ml of tetrahydrofuran at 0°C was added dropwise a solution of 1.0 g (0.002 mol) of **9a** and 0.325 g (0.003 mol) of 3,3-dimethylacrolein in 15 ml of tetrahydrofuran. The mixture was allowed to warm to room temperature and was stirred there for 3 h. The solution was poured into water and the mixture was extracted with methyl t-butyl ether (2x) and methylene chloride (1x). The organic phases were combined, dried over sodium sulfate, then the solvent was removed under reduced pressure. The residual oil was flash chromatographed using 2% methanol/methylene chloride to elute the product, 0.528 g (60%) of **23a**. An analytic sample was crystallized from methylene chloride/methyl t-butyl ether, mp 182-185°C; ir ($CHCl_3$): 1592 cm^{-1}; ^{1}H-nmr: δ 8.43 (dd, J=8 and 2 Hz, 1H), 7.42-7.10 (m, 6H), 6.75-6.37 (m, 2H), 5.80-5.49 (m, 2H), 2.30 (s, 3H), 1.80 (s, broadened, 6H). Anal. Calcd for $C_{22}H_{20}NOF$: C, 79.30; H, 6.00; N, 4.20. Found: C, 79,30; H, 6.30; N, 3.90.

1-(4-Fluorophenyl)-3-(1-methylethyl)-2-(4-methyl-1,3-pentadienyl)-4(1H)-quinolinone (**23b**). This compound was prepared according to the procedure described for **23a** using 1.5 g of **9b**, 0.4 g of 3,3-dimethylacrolein, 0.18 g of sodium hydride (50% in mineral oil), and 0.1 g of 15-crown-5 to give 0.95 g of pure **23b** (70%) as an oil; ir ($CHCl_3$): 1604, 1516 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 8.42 (dd, J=8 and 2 Hz, 1H), 7.42-7.13 (m, 6H), 6.60 (dd, J=8 and 2 Hz, 1H), 6.34 (d, J=10 Hz, 1H), 5.76-5.52 (m, 2H), 3.21 (m, 1H), 1.76 (d, broadened, 6H), 1.47 (d, J=7 Hz, 6H); ms Calcd for $C_{24}H_{24}NOF$: M, 361.1842. Found: M^+, 361.1847.

3-[1-(4-Fluorophenyl)-1,4-dihydro-3-methyl-4-oxoquinolin-2-yl]-(E)-2-propenal (**24a**). Into a solution of 1.0 g (0.003 mol) of **23a** in 250 ml of methylene chloride at -78°C was bubbled ozone for 4 min. Dimethyl sulfide (10 ml) was then added and the mixture was allowed to warm to room temperature and stirred there for 18 h. The solvent was removed under reduced pressure and the residual solid

was flash chromatographed using 2% methanol/methylene chloride to elute the product, 0.23 g (25%) of **24a**, mp 210-212°C [dec]; ir ($CHCl_3$): 1697, 1604, 1503 cm^{-1}; ^{1}H-nmr ($CHCl_3$): δ 9.45 (d, J=7 Hz, 1H), 8.46 (dd, J=8 and 2 Hz, 1H), 7.57-7.10 (m, 6H), 6.90 (d, broadened, 1H), 6.70 (m, 1H), 6.28 (dd, J=16 and 7 Hz, 1H), 2.23 (s, 3H).

3-[1-(4-Fluorophenyl)-1,4-dihydro-3-(1-methylethyl)-4-oxoquinolin-2-yl]-(E)-2-propenal (**24b**). This compound was prepared according to the procedure described for **24a** using 0.9 g of **23b** and an ozonation time of 3 min. to give 0.281 g (34%) of pure **24b**, mp 197-198°C; ir ($CHCl_3$): 1697, 1598, 1509 cm^{-1}; ^{1}H-nmr ($CDCl_3$): δ 9.43 (d, J=7 Hz, 1H), 8.42 (dd, J=8 and 2 Hz, 1H), 7.51-7.00 (m, 6H), 6.96 (d, J=17 Hz, 1H), 6.62 (m, 1H), 6.15 (dd, J=16 and 7 Hz, 1H), 2.98 (m, 1H), 1.47 (d, J=7 Hz, 6H).

7-[1-(4-Fluorophenyl)-1,4-dihydro-3-methyl-4-oxoquinolin-2-yl]-5-hydroxy-3-oxo-(E)-6-heptenoic acid ethyl ester (**25a**). This compound was prepared according to the procedure described for **21a** using 0.22 g of **24a**, 0.22 g of ethyl acetoacetate, 0.34 g of diisopropylamine, and 0.22 g of n-butyllithium to give 0.422 g of **25a** as an oil. This material was used in the following step without purification.

7-[1-(4-Fluorophenyl)-1,4-dihydro-3-(1-methylethyl)-4-oxoquinolin-2-yl]-5-hydroxy-3-oxo-(E)-6-heptenoic acid ethyl ester (**25b**). This compound was prepared according to the procedure described for **21a** using 0.24 g of **24b**, 0.24 g of ethyl acetoacetate, 0.37 g of diisopropylamine, and 0.24 g of n-butyllithium to give 0.63 g of **25b** as an oil. This material was used in the following step without purification.

7-[1-(4-Fluorophenyl)-1,4-dihydro-3-methyl-4-oxoquinolin-2-yl]-(R*,S*)-3,5-dihydroxy-(E)-6-heptenoic acid ethyl ester (**8a**). This compound was prepared according to the procedure described for **7a** using 0.422 g (0.00096 mol) of **25a**, 1.1 ml of 1.0 M triethylborane solution, and 40 mg of sodium borohydride. After methanolysis at room temperature for 48 hr the crude material was flash chromatographed using 4% methanol/methylene chloride to elute the product, 25 mg (10% from **24a**) of as a foam; ^{1}H-nmr ($CDCl_3$): δ 8.43 (dd, J=8 and 2 Hz, 1H), 7.45-7.09 (m, 6H), 6.67 (d, J=4 Hz, 1H), 6.03 (d, J=17.5 Hz, 1H), 5.79 (dd, J=17.5 and 5 Hz, 1H), 4.39 (m, 1H), 4.22 (m, 1H), 4.13 (q, J=7.5 Hz, 2H),

3.72-3.50 (m, broadened, 2H), 2.46 (m, 2H), 2.18 (s, 3H), 1.53-1.35 (m, 2H), 1.24 (t, J=7.5 Hz, 3H).

7-[1-(4-Fluorophenyl)-1,4-dihydro-3-(1-methylethyl)-4-oxoquinolin-3-yl]-(R*,S*)-3,5-dihydroxy-(E)-6-heptenoic acid ethyl ester (**8b**). This compound was prepared according to the procedure described for **7a** using 0.63 g of **25b**, 1.37 ml of 1.0 M triethylborane solution, and 52 mg of sodium borohydride to give 0.177 g (53% from **24b**) of **8b** as a gum; ir ($CHCl_3$): 3518, 1723, 1592, 1218 cm^{-1}; ^1H-nmr ($CDCl_3$): δ 8.40 (dd, J=8 and 2 Hz, 1H), 7.43-7.10 (m, 6H), 6.62 (d, J=4 Hz, 1H), 6.12 (d, J=17.5 Hz, 1H), 5.63 (dd, J=17.5 and 5 Hz, 1H), 4.36 (m, 1H), 4.18 (q, J=4 Hz, 2H), 4.17 (m, 1H), 3.75 (s, broadened, 1H), 3.14 (m, 1H), 3.03 (s, broadened, 1H), 2.45 (m, 2H), 1.41 (d, J=7 Hz, 6H), 1.24 (t, J=7.5 Hz, 3H), 1.35-1.10 (m, 2H); MS Calcd for $C_{27}H_{30}NO_5F$: M, 467.2098. Found: M^+, 467.2087.

7-[1-(4-Fluorophenyl)-1,4-dihydro-3-(1-methylethyl)-4-oxoquinolin-2-yl]-(R*,S*)-3, 5-dihydroxy-(E)-6-heptenoic acid sodium salt (**26b**). To a solution of 127 mg of **8b** in 5 ml of ethanol was added 0.28 ml of 1.0 N sodium hydroxide. After stirring at 60°C for 3 h, the ethanol was removed under reduced pressure. Water (5 ml) was added to the residue and the mixture was washed with methyl t-butyl ether. The aqueous phase was lyopholyzed to produce 83 mg (67%) of **26b**, mp 110-120°C [dec]; ir (KBr): 3413, 1585 cm^{-1}; ^1H-nmr (D_2O): δ 8.13 (dd, J=8 and 2 Hz, 1H), 7.45-7.05 (m, 6H), 6.76 (d, J=4 Hz, 1H), 6.15 (d, J=17.5 Hz, 1H), 5.62 (dd, J=17.5 and 5 Hz, 1H), 4.18-3.97 (m, 2H), 3.53 (m, 1H), 3.13 (m, 1H), 2.17 (m, 2H), 1.50-1.15 (m, 2H), 1.20 (d, J=7 Hz, 6H).

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