

A COUPLING PROCESS FOR PREPARING QUINOLONE INTERMEDIATES

FIELD OF THE INVENTION

The present invention relates to preparation of certain quinolone intermediates. The present invention is related to a process for making a 7-cycloamino-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acids.

BACKGROUND OF THE INVENTION

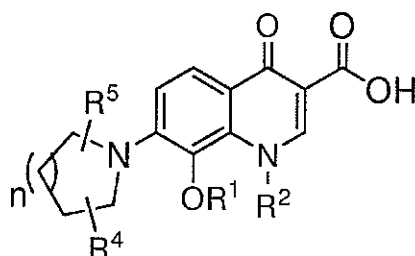
Synthesis of various quinolone compounds have been reported in the literature, e.g., U.S. Patent No. 6,329,391; U.S. Patent No. 6,803,469; B. Ledoussal et al., "Non 6-Fluoro Substituted Quinolone Antibacterials: Structure and Activity", J. Med. Chem., Vol. 35, p. 198-200 (1992); V. Cecchetti et al., "Studies on 6-Aminoquinolines: Synthesis and Antibacterial Evaluation of 6-Amino-8-methylquinolones", J. Med. Chem., Vol. 39, pp. 436-445 (1996); V. Cecchetti et al., "Potent 6-Desfluoro-8-methylquinolones as New Lead Compounds in Antibacterial Chemotherapy", J. Med. Chem., Vol. 39, pp. 4952-4957 (1996)).

The antimicrobial quinolone compounds (3S,5S)-7-[3-amino-5-methyl-piperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid, and (3S,5R)-7-[3-amino-5-methyl-piperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid are disclosed in the U.S. Patent No. 6,329,391, which is herein incorporated by reference in its entirety. However, there is a need in the art for improved methods for preparing these and like antimicrobial compounds.

SUMMARY OF THE INVENTION

The present invention is related to a process for making, e.g. (3S,5S)-7-[3-amino-5-methyl-piperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid, and (3S,5R)-7-[3-amino-5-methyl-piperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid.

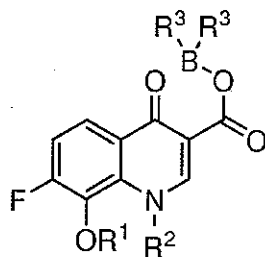
In one embodiment, the invention relates to a process for preparing a substituted quinolone having the Formula (I):



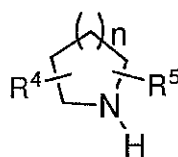
Formula (I);

wherein R¹ is C₁-C₄ alkyl; R² is C₁-C₄ alkyl or C₃-C₆ cycloalkyl; R⁴ and R⁵ are each independently selected from a group consisting of amino, C₁-C₄ alkylamino, protected amino, and C₁-C₄ alkyl; and n is 1 or 2;

the process comprising: reacting a compound of Formula (II) with compounds of Formula (III),
 5 in the presence of a suitable base at about 20°C to about 80°C, followed by hydrolysis:



Formula (II)



Formula (III)

wherein R³ is selected from the group consisting of unsubstituted or substituted C₁-C₄ acyloxy;
 and R¹, R², R⁴, R⁵, and n are as defined for Formula I above.

In another embodiment of the above-described process, for the resulting compound of
 10 Formula I, R¹ is methyl.

In another embodiment of the above-described process, for the resulting compound of
 Formula I, R² is cyclopropyl.

In another embodiment of the above-described process, for the resulting compound of
 Formula I, R⁴ is methyl.

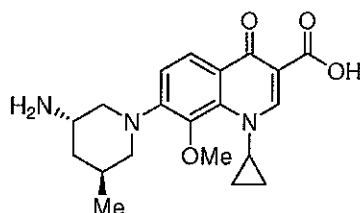
15 In another embodiment of the above-described process, for the compound of Formula II,
 R³ is acetoxy.

In another embodiment of the above-described process, for the compounds of Formula I
 and Formula III, R⁵ is amino.

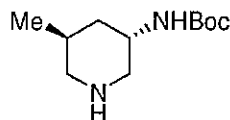
In another embodiment of the above-described process, for the compounds of Formula I and III, R⁵ is amino-*tert*-butoxycarbonyl.

In another embodiment of the above-described process, for the compounds of Formula I and III, R⁵ is amino-*tert*-butoxycarbonyl, and compound I is further subjected to a deprotection
5 process.

In another embodiment of the above-described process, for the resulting compound of Formula I, the compound is:

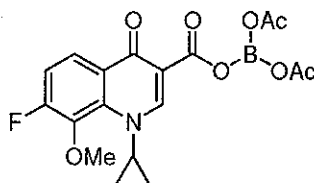


In another embodiment of the above-described process, the compound of Formula (III) is:



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In another embodiment of the above-described process, the compound of Formula (II) is:



In another embodiment of the above-described process, the base is selected from the group consisting of triethylamine, diisopropylethylamine, triisopropylamine, and 1,8-
15 Diazabicyclo[5.4.0]undec-7-ene.

In another embodiment of the above-described process, the base is triethylamine.

DETAILED DESCRIPTION OF THE INVENTION

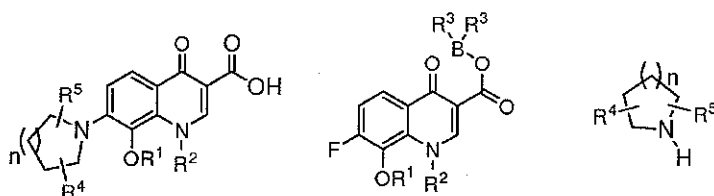
The protecting groups for amino group, or C₁-C₄ alkylamino group include, but are not
20 limited to, carbamate groups, e.g., trichloroethoxycarbonyl, tribromoethoxycarbonyl, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, o-bromobenzyloxycarbonyl, *tert*-amyloxycarbonyl, *tert*-butoxycarbonyl, p-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl; acyl groups, e.g., C₁-C₄ haloacetyl groups such as (mono-, di-, or

tri-) bromoacetyl, (mono-, di-, or tri-) chloroacetyl, and (mono-, di-, or tri-) fluoroacetyl; arylalkyl groups, e.g., benzyl, diphenylmethyl, and trityl.

In one embodiment, the amino protecting group is *tert*-butoxycarbonyl.

Herein is described a process for the preparation of a substituted quinolone as depicted in
5 general Formula I, wherein R^1 is C_1 - C_4 alkyl, R^2 is C_1 - C_4 alkyl or C_3 - C_6 cycloalkyl, and R^4 and R^5 are each independently selected from a group consisting of amino, C_1 - C_4 alkylamino, protected amino, and C_1 - C_4 alkyl. A boron ester chelate of the 7-fluoroquinolone acid as depicted in general Formula II, wherein R^1 , R^2 , are as defined for Formula I, R^3 is selected from the group consisting of unsubstituted or substituted C_1 - C_4 acyloxy, fluorine, chlorine, and
10 bromine, is charged to a reactor. The solid is diluted with a solution of a suitable cyclic amine side chain as depicted in general Formula III, wherein R^4 and R^5 are as defined, and n is 1 or 2; and a tertiary amine base, in a suitable organic solvent for the coupling reaction to take place. The coupling reaction is kept between about 20°C to about 80°C until complete. The completion of the reaction may be determined by HPLC, TLC, or IR spectroscopy analyses that
15 are known to one skilled in the art. The reaction solvent is partially removed by distillation to reduce the volume and the reaction is then diluted with an aqueous caustic solution to initiate hydrolysis of the boron ester chelate. Distillation, with heating, may be continued under vacuum for about 2 to 6 hours or until no further distillates are observed. The reaction progress may be monitored by HPLC, TLC, or IR spectroscopy. Upon completion, the reaction is neutralized by
20 the addition of an acid until a pH of about 7 or below is achieved. An organic, water immiscible solvent, e.g., dichloromethane, is added to the reaction mixture, and agitation followed by phase separation is performed. The organic phase is removed and this extractive process is repeated, if desired. The organic extracts are charged to a reactor, concentrated to approximately 50% volume, if desired, and treated with an aqueous acid, e.g., hydrochloric acid, to effect protecting
25 group removal, e.g., *tert*-butoxycarbonyl (Boc) group. The progress of the deprotection reaction may be monitored by HPLC, TLC, or IR spectroscopy. When the reaction is complete, the biphasic mixture is allowed to separate. The organic phase is removed from the reactor and extraction with additional organic solvent may be performed. The acidified aqueous phase is diluted with water and residual organic solvent is removed. The pH of the reaction solution is
30 adjusted to between about 7 to about 8 with aqueous caustic while keeping the temperature at about 30°C to about 70°C. The precipitated solids are allowed to stir at about 40°C to about 60°C for at least about an hour and are then cooled. The solids may be isolated by suction

filtration and washed with water. The solid product may be dried in a vacuum oven at about 40°C to about 60°C to afford yields typically in the range of about 70-90%.



Formula (I)

Formula (II)

Formula (III)

- 5 The reactant of Formula III is as defined above. In one embodiment, III is a piperidine. In another embodiment, III is (3S,5S)-3-amino-5-methylpiperidine. In another embodiment, III is (3S,5S)-(5-Methyl-piperidin-3-yl)-carbamic acid *tert*-butyl ester.

In one embodiment, R⁴ is a methyl.

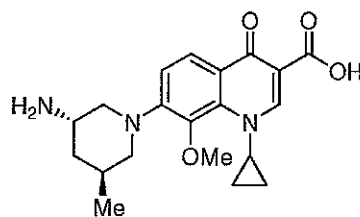
In one embodiment, R⁵ is amino-*tert*-butoxycarbonyl.

- 10 In another embodiment, R⁵ is amino.

In one embodiment, R¹ is methyl.

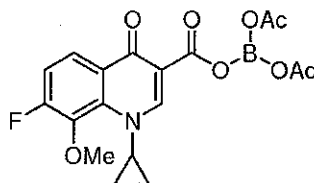
In one embodiment, R² is cyclopropyl.

In another embodiment of the above-described process, for the resulting compound of Formula I, the compound is:



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In another embodiment of the above-described process, the compound of Formula II is:



- 20 The solvent which may be used in this reaction is not limited as far as it does not adversely affect the reaction, and includes, but is not limited to, nitriles such as acetonitrile; amides such as N,N-dimethylformamide, N,N-dimethylacetamide; pyrrolidinones, such as N-

methyldipyrrolidinone; sulfoxides such as dimethyl sulfoxide, ethers, e.g., methyl *tert*-butyl ether (MTBE), dimethoxy ethane (DME), diethyl ether, tetrahydrofuran, diisopropyl ether, dioxane, anisole, diethylene glycol diethyl ether; aromatic hydrocarbons such as benzene, toluene, xylene; halogenated hydrocarbons such as dichloromethane, chloroform; and esters such as ethyl acetate, butyl acetate. These solvents may be used in admixture. In one embodiment, the solvent is acetonitrile.

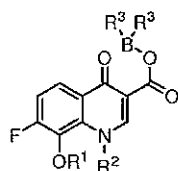
The bases that may be used in this reaction include, but are not limited to, alkyl amines such as DIPEA (Diisopropylethylamine), N-alkylmorpholines, N-alkylpyrrolidines, N-alkylpiperidines, tertiary diazabicyclic amines such as DBU (1,8-Diazabicyclo[5.4.0]undec-7-ene), DABCO 1,4-Diazabicyclo[2.2.2]octane), and DBN (1,5-Diazabicyclo[4.3.0]non-5-ene), substituted and non-substituted aromatic amines such as pyridine, DMAP (N,N-diethylaminopiperidine), pyrimidine, N-alkylpyrrole, N-alkylimidazole, N-alkylcarbazole, N-alkylindole, and triazine, guanidine bases such as tetraalkyl guanidines, and N,N-dialkylpiperazines. In one embodiment, the base is selected from the group consisting of triethylamine, diisopropylethylamine, triisopropyl amine, and 1,8-Diazabicyclo[5.4.0]undec-7-ene. In another embodiment, the base is triethylamine.

The amount of the base used may be about 1 to about 4 molar amount of the compound of the general Formula III or its salt.

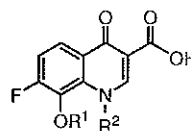
The amount of the compound of the general Formula II or its salt used may be about 0.8 to 1.5 molar amount of the compound of the general Formula III or its salt.

Herein is also described a process for the preparation of a boronate ester of 7-fluoroquinolone as depicted below in general Formula II. Boron oxide is treated with an organic carboxylic acid R^3CO_2H and carboxylic anhydride $(R^3CO)_2O$ wherein R^3 is selected from the group consisting of unsubstituted or substituted C_1 - C_4 alkyl. The mixture is heated at about 90°C to about 130°C for about 1 to about 4 hours, cooled to about 20°C to about 90°C and a functionalized 7-fluoroquinolone as depicted in general Formula IV, is added. For the 7-fluoroquinolone of general Formula IV, R^1 is C_1 - C_4 alkyl, and R^2 is C_1 - C_4 alkyl or C_3 - C_8 cycloalkyl. The reaction is again heated at about 90°C to about 130°C for about 3 to about 9 hours and then cooled. An aromatic solvent, e.g., toluene, is then added to the reaction. Another solvent, e.g., *tert*-butylmethyl ether, is then added to the reaction mixture to afford precipitation of the product. After cooling to about 0 to about 25°C, the product is removed via filtration and

washed with ether. The solid product is dried in a vacuum oven to afford yields typically in the range of 70-90%.



Formula (II)



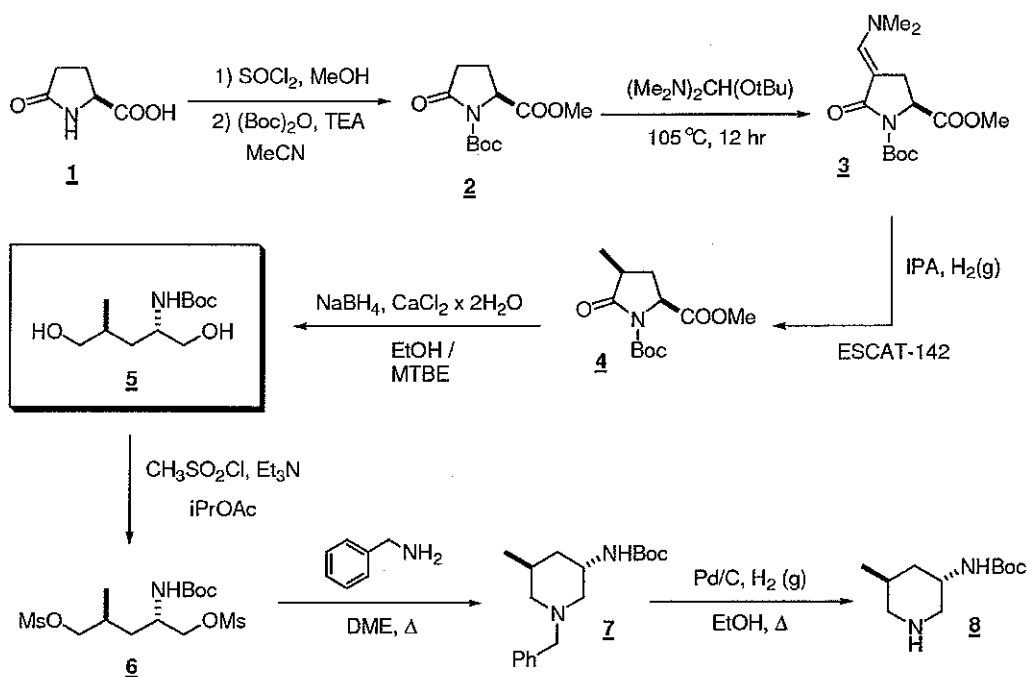
Formula (IV)

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EXAMPLES:

Example 1: Synthesis of (3S,5S)-7-[3-amino-5-methyl-piperidinyl]-1-cyclopropyl-1,4-dihydro-
10 8-methoxy-4-oxo-3-quinolinecarboxylic acid and malate salt thereof.

A. Synthesis of (3S,5S)-(5-Methyl-piperidin-3-yl)-carbamic acid *tert*-butyl ester (8):



15 (2S)-1-(1,1-Dimethylethyl)-5-oxo-1,2-pyrrolidinedicarboxylic acid-2-methyl ester, (2). A 50-L reactor is charged with compound (1) (5.50 Kg, 42.60 mol), methanol (27 L) and cooled to 10-

15°C. Thionyl chloride (10.11 Kg, 2.0 equiv.) is added via addition funnel over a period of 65 min, with external cooling to maintain temperature at < 30°. The resulting solution is stirred at 25°C + 5°C for 1.0 hour, after which the methanol is distilled off under reduced pressure. The resulting thick oil is azeotroped with ethyl acetate (3 x 2.5 L) to remove residual methanol. The
5 residue is dissolved in ethyl acetate (27.4 L), charged into a 50 L reactor, and neutralized by the addition of triethylamine (3.6 Kg) from an addition funnel over 30 minutes. The temperature of the neutralization is maintained below 30°C via external cooling. The resulting suspension of triethylamine hydrochloride is removed by filtration, and the clarified mother liquor solution is charged to a 50 L reactor, along with DMAP (0.53 Kg). Di-*tert*-butyl dicarbonate (8.43 Kg) is
10 added via hot water heated addition funnel, over a period of 30 min with external cooling to maintain temperature at about 20-30°C. The reaction is complete after 1 hour as determined by TLC analysis. The organic phase is washed with ice cold 1N HCl (2 x 7.5 L), saturated sodium bicarbonate solution (1 x 7.5 L), and dried over magnesium sulfate. The mixture is filtered through a nutsche filter and ethyl acetate is removed under reduced pressure to yield a crystalline
15 slurry that is triturated with MTBE (10.0 L) and filtered to afford intermediate (2) as a white solid (5.45 Kg, 52.4%). Anal. Calcd for C₁₁H₁₇NO₅: C, 54.3; H, 7.04; N, 5.76. Found: C, 54.5; H, 6.96; N, 5.80. HRMS (ESI⁺) Expected for C₁₁H₁₈NO₅, [M+H] 244.1185. Found 244.1174; ¹H NMR (CDCl₃, 500 MHz): δ=4.54 (dd, *J* = 3.1, 9.5 Hz, 1H), 3.7 (s, 3H), 2.58-2.50 (m, 1H), 2.41 (ddd, 1H, *J* = 17.6, 9.5, 3.7), 2.30-2.23 (m, 1H), 1.98-1.93 (m, 1H), 1.40 (s, 9H); ¹³C NMR
20 (CDCl₃, 125.70 MHz) δ 173.3, 171.9, 149.2, 83.5, 58.8, 52.5, 31.1, 27.9, 21.5; Mp 70.2°C.

(2S,4E)-1-(1,1-Dimethylethyl)-4-[(dimethylamino)methylene]-5-oxo-1,2-pyrrolidinedicarboxylic acid-2-methyl ester (3). A 50-L reactor is charged with intermediate (2) (7.25 Kg, 28.8 mol), DME (6.31 Kg), and Brederick's Reagent (7.7 Kg, 44.2 mole). The
25 solution is agitated and heated to 75°C ± 5°C for at least three hours. The progress of the reaction is monitored by HPLC. The reaction is cooled to 0°C ± 5°C over one hour during which time a precipitate forms. The mixture is held at 0°C ± 5°C for one hour and filtered through a nutsche filter and the product dried in a vacuum oven for at least 30 hours at 30°C ± 5°C to give intermediate (3) as a white crystalline solid (6.93 Kg, 77.9%). Anal. Calcd for C₁₄H₂₂N₂O₅: C,
30 56.4; H, 7.43; N, 9.39. Found C, 56.4; H, 7.32; N, 9.48; HRMS (ESI⁺) Expected for C₁₄H₂₂N₂O₅, [M+H] 299.1607. Found 299.1613; ¹H NMR (CDCl₃, 499.8 MHz) δ = 7.11 (s, 1H), 4.54 (dd, 1H, *J* = 10.8, 3.6), 3.74 (s, 3H), 3.28-3.19 (m, 1H), 3.00 (s, 6H), 2.97-2.85

(m, 1H), 1.48 (s, 9H); ^{13}C NMR (CDCl_3 , 125.7 MHz) δ = 172.6, 169.5, 150.5, 146.5, 90.8, 82.2, 56.0, 52.3, 42.0, 28.1, 26.3. Mp 127.9°C.

(2S,4S)-1-(1,1-Dimethylethyl)-4-methyl-5-oxo-1,2-pyrrolidinedicarboxylic acid-2-methyl ester

- 5 (4). A 10-gallon Pfaudler reactor is inerted with nitrogen and charged with ESCAT 142 5% palladium powder on carbon (50% wet, 0.58 Kg wet wt.), intermediate (3) (1.89 Kg, 6.33 mol) and isopropanol (22.4 Kg). The reaction mixture is agitated under a 45-psi hydrogen atmosphere at 45°C for 18 hrs. The reaction mixture is then cooled to room temperature and filtered through a bed of Celite (0.51 Kg) in a nutsche filter to remove catalyst. The mother liquor is evaporated under reduced pressure to give a thick oil that crystallizes on standing to afford 4 (1.69 Kg, 100%) as a 93:7 diastereomeric mixture. A sample of product mixture is purified by preparative HPLC to give material for analytical data. Anal. Calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_5$: C, 56.0; H, 7.44; N, 5.44. Found C, 55.8; H, 7.31; N, 5.44; MS (ESI⁺) Expected for $\text{C}_{12}\text{H}_{19}\text{NO}_5$, [M+H] 258.1342. Found 258.1321; ^1H NMR (CDCl_3 , 499.8 MHz) δ = 4.44 (m, 1H), 3.72 (s, 3H), 2.60-2.48 (m, 2H), 1.59-1.54 (m, 1H), 1.43 (s, 9H), 1.20 (d, j = 6.8 Hz, 3H); ^{13}C NMR (CDCl_3 , 125.7 MHz) δ = 175.7, 172.1, 149.5, 83.6, 57.4, 52.5, 37.5, 29.8, 27.9, 16.2. Mp 89.9°C.
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- (1S,3S)-(4-Hydroxyl-1-hydroxymethyl-3-methyl-butyl)-carbanic acid *tert*-butyl ester (5). A 50-L reactor is charged with intermediate (4) (3.02 Kg, 11.7 mol), absolute ethanol (8.22 Kg), and MTBE (14.81 Kg). The solution is agitated and cooled to 0°C $\pm$ 5°C and sodium borohydride (1.36 Kg, 35.9 mol) is added in small portions so as to maintain reaction temperature at 0°C $\pm$ 5°C. A small amount of effervescence is observed. The reaction mixture is warmed to 10°C $\pm$ 5°C and calcium chloride dihydrate (2.65 Kg) is added portion wise at a slow rate over an hour so as to maintain a reaction temperature of 10°C $\pm$ 5°C. The reaction is allowed to warm to 20°C $\pm$ 5°C over one hour and agitated for an additional 12 hours at 20°C $\pm$ 5°C. The reaction is cooled to -5°C $\pm$ 5°C, ice-cold 2N HCl (26.9 Kg) is added at a rate to maintain a reaction temperature of 0°C $\pm$ 5°C. Agitation is stopped to allow phases to separate. The lower aqueous phase (pH = 1) is removed. The reactor is charged with aqueous saturated sodium bicarbonate (15.6 Kg) over five minutes. Agitation is stopped to allow phases to separate. The lower aqueous phase (pH = 8) is removed. The reactor is charged with magnesium sulfate (2.5 Kg) and agitated for at least 10 minutes. The mixture is filtered through a nutsche filter, and condensed under reduced pressure to afford intermediate (5) (1.80 Kg, 66%). Anal. Calcd for
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$C_{11}H_{23}NO_4$: C, 56.6 H, 9.94; N, 6.00. Found C, 56.0; H, 9.68; N, 5.96; HRMS (ESI⁺) Expected for $C_{11}H_{24}NO_4$, [M+H] 234.1705. Found 234.1703; ¹H NMR (CDCl₃, 500 MHz) δ = 6.34 (d, J = 8.9 Hz, 1H, NH), 4.51 (t, J = 5.8, 5.3 Hz, 1H, NHCHCH₂OH), 4.34 (t, J = 5.3, 5.3 Hz, 1H, CH₃CHCH₂OH), 3.46-3.45, (m, 1H, NHCH), 3.28 (dd, J = 10.6, 5.3 Hz, NHCHCHHOH), 3.21 (dd, J = 10.2, 5.8 Hz, 1H, CH₃CHCHHOH), 3.16 (dd, J = 10.2, 6.2 Hz, 1H, NHCHCHHOH), 3.12 (dd, J = 10.6, 7.1 Hz, 1H, CH₃CHCHHOH), 1.53-1.50 (m, 1H, CH₃CHCHHOH), 1.35 (s, 9H, O(CH₃)₃), 1.30 (ddd, J = 13.9, 10.2, 3.7 Hz, 1H, NHCHCHCH), 1.14 (ddd, J = 13.6, 10.2, 3.4 Hz, 1H, NHCHCHCH), 0.80 (d, J = 6.6 Hz, 3H, CH₃); ¹³C NMR (CDCl₃, 125.7 MHz) δ 156.1, 77.9, 50.8, 65.1, 67.6, 65.1, 35.6, 32.8, 29.0, 17.1. Mp 92.1°C.

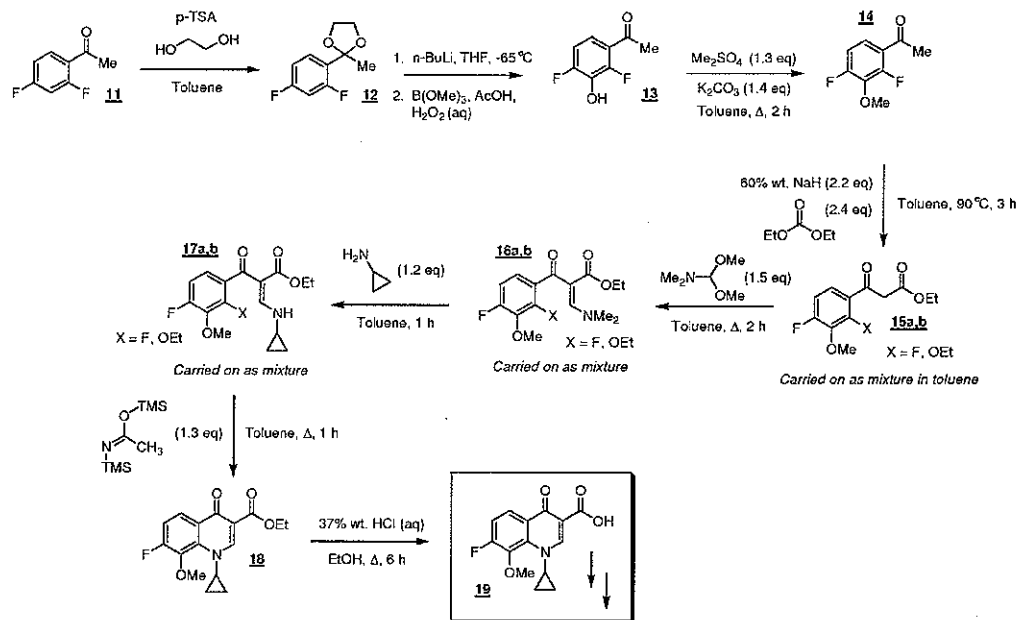
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(2S,4S)-Methanesulfonic acid 2-*tert*-butoxycarbonylamino-5-methanesulfonyloxy-4-methyl-pentyl ester (6). A 50 L reactor is charged with a solution of intermediate (5) (5.1 Kg) in isopropyl acetate (i-PrOAc) 11.8 Kg followed by a rinse with an additional 7.9 Kg i-PrOAc. The reaction is cooled to 15°C $\pm$ 5°C and triethylamine (TEA) (7.8 Kg) is added while maintaining the set temperature. The reactor is further cooled to 0°C $\pm$ 5°C and methanesulfonyl chloride (MsCl) (6.6 Kg) is added to the reaction solution while maintaining the set temperature. The reaction is stirred for a few hours and monitored for completion by HPLC or TLC. The reaction is quenched by the addition of a saturated aqueous bicarbonate solution and the resulting isolated organic phase is washed successively with cold 10% aqueous triethylamine solution, cold aqueous HCl solution, cold saturated aqueous bicarbonate solution, and finally saturated aqueous brine solution. The organic phase is dried, filtered, and concentrated in vacuo below 55°C $\pm$ 5°C until a solid / liquid slurry containing intermediate (6) is obtained. The slurry is used crude in subsequent reaction without further characterization.

25 (3S,5S)-(1-Benzyl-5-methyl-piperidin-3-yl)-carbamic acid *tert*-butyl ester (7). A 50 L reactor is charged with 9.1 Kg of neat benzylamine. The reactor is brought to 55°C and a solution of intermediate (6) (8.2 Kg) in 1,2-dimethoxyethane (DME) (14.1 Kg) is added to the reactor while maintaining a temperature of 60°C $\pm$ 5°C. After complete addition of this solution, the reaction is stirred at 60°C $\pm$ 5°C for several hours and monitored for completion by TLC or HPLC. The reaction is cooled to ambient temperature and volatiles (DME) are removed by rotary evaporation under vacuum. The residue is diluted with 11.7 Kg of 15% (v/v) ethyl acetate/hexanes solution and treated, while agitating, with 18.7 Kg of 20% (wt) aqueous

- potassium carbonate solution. A triphasic mixture is obtained upon settling. The bottom aqueous phase is removed and the middle phase is set aside. The upper organic phase is collected and held for combination with extracts from additional extractions. The isolated middle phase is extracted twice again with 11.7 Kg portions of 15% (v/v) ethyl acetate/hexanes solution, each time combining the extracts with original organic phase. The combined organic extracts are transferred into a rotary evaporator and solvent is removed under vacuum until an oily residue remains. The residue is then purified via large-scale preparative chromatography to afford purified intermediate (7) as an oil.
- 10 (3S,5S)-(5-Methyl-piperidin-3-yl)-carbamic acid *tert*-butyl ester (8). A 40 L pressure vessel is charged with 0.6 Kg 50% wet, solid palladium on carbon (E101, 10 wt. %) under flow of nitrogen. A solution of 3.2 Kg intermediate (7) in 13.7 Kg of absolute ethanol is then charged to the reactor under nitrogen. The reactor is purged with nitrogen and is then pressurized with hydrogen at 45 psi. The reaction is then heated to 45°C while maintaining a hydrogen pressure of 45 psi. The reaction is monitored by TLC or LC until complete. The reaction is cooled to ambient temperature, vented, and purged with nitrogen. The reactor contents are filtered through a bed of Celite and the solids are washed with 2.8 Kg of absolute ethanol. The filtrate is concentrated by rotary evaporation under vacuum until a waxy solid is obtained to afford intermediate (8): TLC R_f (Silica F₂₅₄, 70:30 v/v ethyl acetate-hexanes, KMnO₄ stain) = 0.12; ¹H NMR (300 MHz, CDCl₃) δ 5.31 (br s, 1H), 3.80-3.68 (m, 1H), 2.92 (d, J =11.4 Hz, 1H), 2.77 (AB quart, J_{AB} =12.0 Hz, $\Delta\nu$ =50.2 Hz, 2H), 2.19 (t, J =10.7 Hz, 1H), 1.82-1.68 (m, 2H), 1.54 (br s, 1H), 1.43 (s, 9H), 1.25-1.15 (m, 1H), 0.83 (d, J =6.6 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 155.3, 78.9, 54.3, 50.8, 45.3, 37.9, 28.4, 27.1, 19.2; MS (ESI+) m/z 215 (M+H), 429 (2M+H).
- 25 B. Synthesis of 1-Cyclopropyl-7-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (19):

12



68% overall from 13

- Intermediate (12): A reactor is charged with a solution of intermediate (11) (1.2 Kg, 7.7 mol, 1.0 eq) in anhydrous toluene (12 L) followed by ethylene glycol (1.8 L, 15.7 mol, 4.2 eq) and solid p-toluenesulfonic acid (120 g, 10 wt. %). The reaction mixture is stirred at ambient temperature for at least 30 minutes and then heated to reflux, collecting the water/toluene azeotrope in a Dean Stark type trap apparatus until the reaction is complete as determined by TLC analysis (15% EtOAc/Hexanes v/v). Upon completion, the reaction is cooled to ambient temperature and poured into an aqueous solution of sodium bicarbonate (6 L). The organic toluene phase was removed and washed with saturated sodium bicarbonate solution (6 L), distilled water (2 x 6 L), and saturated aqueous brine (6 L). The organic phase was removed and dried over MgSO₄, filtered, and evaporated under reduced pressure to afford intermediate (12) as an oil (1.3 Kg, 86%). The material is used without further purification in subsequent reaction steps.
- Intermediate (13): A reactor is charged with a solution of intermediate (12) (1.2 Kg, 6.0 mol, 1.0 eq) in anhydrous tetrahydrofuran (12 L) and n-butyllithium (2.5M in hexanes, 2.6 L, 6.6 mol, 1.1 eq) is added at -40°C, while maintaining this temperature throughout the addition. The reaction is stirred for at least one hour at -40°C and trimethylborate (0.9 L, 7.8 mol, 1.3 eq) is added to the mixture while maintaining the temperature at or below -40°C. The reaction mixture is stirred for at least one hour at -40°C until complete as determined by TLC analysis (30%

EtOAc/Hexanes v/v). The reaction is warmed slightly to -30°C and acetic acid (3 L) is added slowly. Upon complete addition, water is added (0.5 L) to the reaction and the mixture is allowed to quickly warm to ambient temperature while stirring overnight. Organic solvent is removed from the reaction by distillation under reduced pressure at 45°C. To the reaction residue
5 is added 3-4 volumes of water (6 L) and 30% hydrogen peroxide (0.7 L, 1.0 eq) slowly at ambient temperature with cooling provided to control the exotherm. The reaction is stirred for at least an hour at ambient temperature until complete as determined by TLC (15% EtOAc/Hexanes v/v). The reaction mixture is cooled to 0-5°C and excess peroxide is quenched with the addition of 10% aqueous sodium bisulfite solution (2 L). The mixture is tested to ensure
10 a negative peroxide result and the reaction is acidified by the addition of 6N HCl (aq) (1.2 L). The reaction is stirred until the hydrolysis reaction is complete as determined by TLC or NMR analysis. The resulting solids are collected by suction filtration to afford intermediate (13) as a yellow solid (1.0 Kg, 79%).

15 Intermediate (14): A reactor is charged with intermediate (13) (0.53 Kg, 3.0 mol, 1.0 eq) and dissolved in dry toluene (2.7 Kg, 3.1 L). To this solution is added dimethylsulfate (0.49 Kg, 3.9 mol, 1.30 eq) followed by solid potassium carbonate (0.58 Kg, 4.2 mol, 1.4 eq). The reaction mixture is heated to reflux and held for at least 1 hour until complete as determined by HPLC. During this time, vigorous gas evolution is observed. The reaction is then cooled to ambient
20 temperature and diluted with distilled water (3.2 L) along with 30% NaOH (aq) (0.13 Kg, 0.33 eq). The aqueous phase is separated and the remaining toluene phase is extracted twice more with distilled water (3.2 L) combined with 30% NaOH (aq) (0.13 Kg, 0.33 eq), removing the aqueous phase each time. The organic upper phase is concentrated by distillation in vacuo (< 100 mbar) at approximately 40°C until a concentrated toluene solution is achieved. The resulting
25 solution is cooled to ambient temperature, checked for quality and yield by HPLC, and carried forward to the next step in the synthesis without further purification (theoretical yield for intermediate (14) assumed, 0.56 Kg).

Intermediate (15a,b): A reactor is charged with 1.8 Kg (2.1 L) anhydrous toluene along with
30 sodium hydride (0.26 Kg, 6.6 mol, 2.20 eq) as a 60 wt. % dispersion in mineral oil. To this mixture is added (0.85 Kg, 7.2 mol, 2.4 eq) diethylcarbonate as the reaction mixture is heated to 90°C over 1 hour. A solution of intermediate (14) (~1.0 eq) in toluene from the previous step is

added to the reaction while maintaining a temperature of $90^{\circ}\text{C} \pm 5^{\circ}\text{C}$. Gas evolution can be observed during this addition. After complete addition, the reaction is stirred for at least 30 minutes or until complete as determined by HPLC analysis. Upon completion, the mixture is cooled to ambient temperature and diluted with 10 wt. % aqueous sulfuric acid (3.8 Kg, 3.9 mol, 1.3 eq) with agitation. The phases are allowed to separate and the lower aqueous phase is removed. The remaining organic phase is concentrated in vacuo (<100 mbar) at approximately 40°C until a concentrated toluene solution is achieved. The resulting solution is cooled to ambient temperature and carried forward to the next step in the synthesis without further purification (theoretical yield for intermediate (15a,b) assumed, 0.85 Kg).

10

Intermediate (16a,b; 17a,b): A reactor is charged with a solution of intermediate (15a,b) (0.85 Kg, ~ 3.0 mol, ~ 1.0 eq) in toluene from the previous step. To the reactor is then added dimethylformamide-dimethylacetal (0.54 Kg, 4.5 mol, 1.5 eq) and the resulting solution is heated to reflux temperature (~ 95 - 105°C). The lower boiling solvent (methanol from reaction) is allowed to distill off while the temperature is maintained at $\geq 90^{\circ}\text{C}$. Heating is continued for at least 1 hour or until complete as determined by HPLC analysis. Upon completion, the reaction containing the mixture of intermediate (16a,b), is cooled to ambient temperature and toluene (1.8 Kg, 2.1 L) along with cyclopropylamine (0.21 Kg, 3.6 mol, 1.2 eq) are added to the reaction. The reaction is stirred at ambient temperature for at least 30 minutes until complete as determined by HPLC. Upon completion, the reaction is diluted with 10 wt. % aqueous sulfuric acid (2.9 Kg, 3.0 mol, 1.0 eq) with agitation, and the phases are then allowed to separate. The aqueous phase is removed and the organic phase is concentrated under reduced pressure (<100 mbar) at approximately 40°C by distillation. When the desired concentration is achieved, the solution is cooled to ambient temperature and the toluene solution containing the mixture of intermediate (17a,b) is carried forward to the next step in the synthesis without further purification (theoretical yield for intermediate (17a,b) assumed, ~ 1.1 Kg).

25

Intermediate (18): A reactor is charged with a solution of the mixture of intermediate (17a,b) (~ 4.7 Kg, ~ 3.0 mol) at ambient temperature. To the reactor is added N,O-bis(trimethylsilyl)acetamide (0.61 Kg, 3.0 mol, 1.0 eq) and the reaction is heated to reflux temperature (~ 105 - 115°C) for at least 30 minutes or until complete as determined by HPLC analysis. If not complete, an additional amount of N,O-bis(trimethylsilyl)acetamide (0.18 Kg, 0.9

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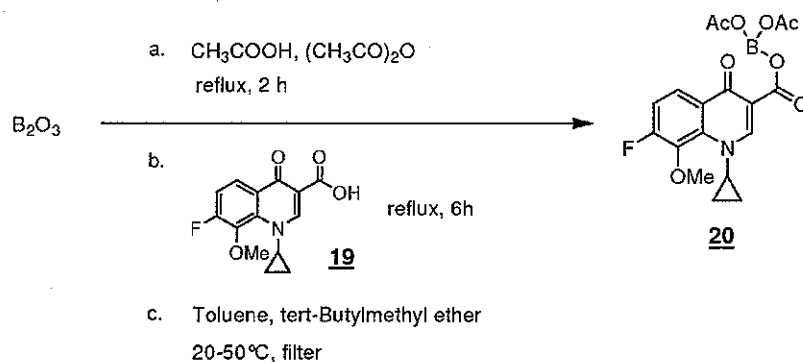
15

mol, 0.3 eq) is added to the reaction to achieve completion. Upon completion, the reaction is cooled to below 40°C and organic solvent is removed under reduced pressure (<100 mbar) at approximately 40°C by distillation until a precipitate is formed. The reaction is cooled to ambient temperature and the precipitated solids are isolated by suction filtration and washed
 5 with distilled water twice (1 x 1.8 L, 1 x 0.9 L). The solid is dried to afford intermediate (18) as a white solid (0.76 Kg, 82%). The material is used without further purification in the next reaction step.

Intermediate (19): A reactor is charged with solid intermediate (18) (0.76 Kg, ~2.5 mol, ~1.0
 10 eq) at ambient temperature followed by ethanol (5.3 Kg, 6.8 L) and 32 wt. % aqueous hydrochloric acid (1.1 Kg, 10 mol). The reaction mixture is brought to reflux temperature (76-80°C) during which time the mixture first becomes homogeneous and later becomes heterogeneous. The mixture is heated at reflux for at least 5 hours or until complete as determined by TLC analysis (15% EtOAc/Hexanes v/v). Upon completion, the reaction is cooled
 15 to 0°C ± 5°C and the precipitated solid is isolated by filtration and washed with distilled water (1.7 Kg) followed by ethanol (1.7 Kg). The isolated solid is dried to afford intermediate (19) as a white solid (0.65 Kg, ~95%). ¹H NMR (CDCl₃, 300 MHz) δ (ppm): 14.58 (s, 1H), 8.9 (s, 1H), 8.25 (m, 1H), 7.35 (m, 1H), 4.35 (m, 1H), 4.08 (s, 3H), 1.3 (m, 2H), 1.1 (m, 2H). ¹⁹F NMR (CDCl₃ + CFCl₃, 292 MHz) δ (ppm): -119. HPLC: 99.5% by area.

20

C. Synthesis of borone ester chelate of 1-Cyclopropyl-7-fluoro-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (20):



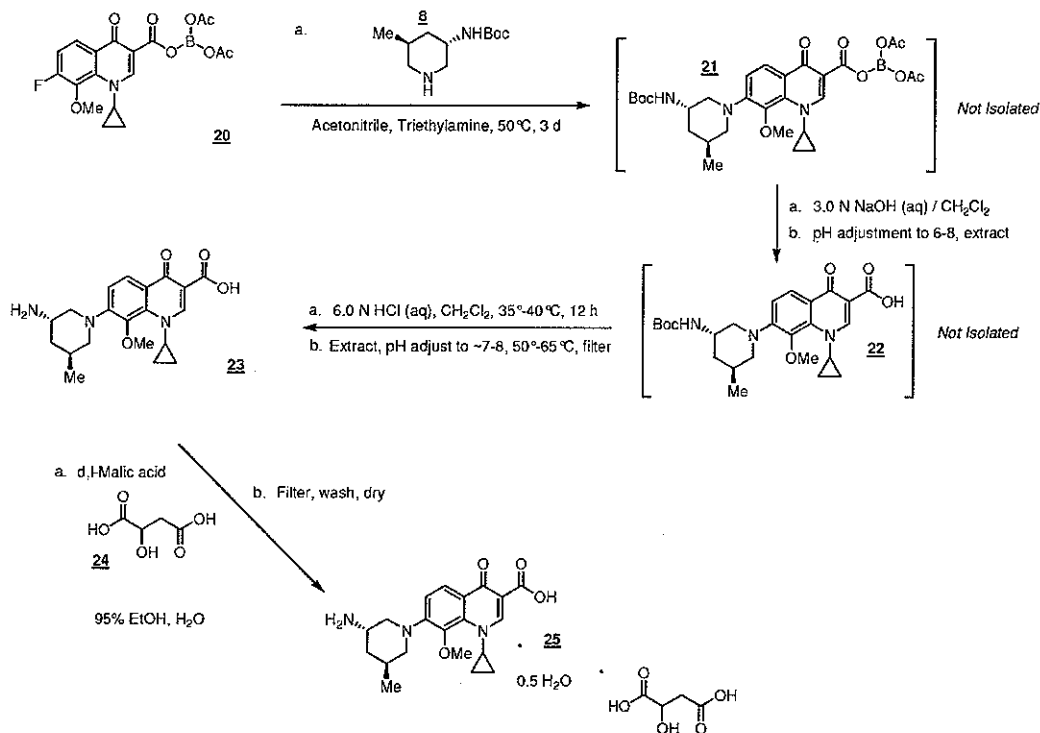
25 A reactor is charged with boron oxide (2.0 Kg, 29 mol) followed by dilution with glacial acetic acid (8.1 L, 142 mol) and acetic anhydride (16.2 L, 171 mol). The resulting mixture is heated to

reflux temperature for at least 2 hours. The reaction contents are cooled to 40°C and the solid 7-fluoroquinolone acid intermediate (19) (14.2 Kg, 51 mol) is added to the reaction mixture. The mixture is again heated to reflux temperature for at least 6 hours. Reaction progress is monitored by HPLC and NMR. The mixture is cooled to approximately 90°C and toluene (45 L) is added to the reaction. The reaction is further cooled to 50°C and *tert*-butylmethyl ether (19 L) is added to the reaction mixture to bring about precipitation of the product. The mixture is then cooled to 20°C and the solid product (19) is isolated by filtration. The isolated solids are then washed with *tert*-butylmethyl ether (26 L) prior to drying in a vacuum oven at 40°C (50 torr). The product yield obtained for intermediate (20) in this reaction is 86.4%. Raman (cm⁻¹): 3084.7, 3022.3, 2930.8, 1709.2, 1620.8, 1548.5, 1468.0, 1397.7, 1368.3, 1338.5, 1201.5, 955.3, 653.9, 580.7, 552.8, 384.0, 305.8. NMR (CDCl₃, 300 MHz) δ (ppm): 9.22 (s, 1H), 8.38-8.33 (m, 1H), 7.54 (t, *J*=9.8 Hz, 1H), 4.38-4.35 (m, 1H), 4.13 (s, 3H), 2.04 (s, 6H), 1.42-1.38 (m, 2H), 1.34-1.29 (m, 2H). TLC (Whatman MKC18F Silica, 60Å, 200 μ m), Mobile Phase: 1:1 (v/v) CH₃CN : 0.5N NaCl (aq), UV (254/366 nm) visualization; R_f=0.4-0.5.

15

D. Coupling of 1-Cyclopropyl-7-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid (20) to (3S, 5S)-(5-Methyl-piperidin-3-yl)-carbamic acid *tert*-butyl ester (8), and synthesis of malate salt of (3S,5S)-7-[3-amino-5-methyl-piperidinyl]-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-3-quinolinecarboxylic acid (25):

17



A reactor is charged with solid intermediate (20) (4.4 Kg, 10.9 mol) followed by dilution with a solution of triethylamine (TEA) (2.1 L, 14.8 mol) and piperidine side chain intermediate (8) (2.1 Kg, 9.8 mol) in acetonitrile (33.5 L, 15.7 L/Kg) at room temperature. The resulting mixture is warmed to approximately 50°C until reaction is judged complete. Reaction progress is monitored by HPLC or reverse phase TLC. When complete, the reaction is cooled to approximately 35°C and reaction volume is reduced to approximately half by distillation of acetonitrile under vacuum between 0-400 torr. The reactor is then charged with 28.2 Kg of 3.0N NaOH (aq) solution and the temperature is raised to approximately 40°C. Distillation under vacuum is continued between 1-4 hours or until no further distillates are observed. The reaction is then cooled to room temperature and the hydrolysis reaction is monitored by HPLC or reverse phase TLC. Upon completion, the reaction mixture is neutralized to a pH of between 6-8 by adding ~4-5 Kg of glacial acetic acid. The reactor is then charged with 12.7 Kg (9.6 L) of dichloromethane as an extraction solvent, the mixture is agitated, phases are allowed to separate, and the organic dichloromethane phase is removed. The extraction process is repeated two additional times using 12.7 Kg (9.6 L) of dichloromethane, collecting the lower, organic phase each time. The aqueous phase is discarded and the organic extracts are combined in a single

reactor. The reactor contents are heated to 40°C and the reaction volume is reduced to approximately one half by distillation. The reactor is then charged with 20.2 Kg 6.0N HCl (aq) solution, the temperature is adjusted to 35°C, and agitation is allowed for at least 12 hours to permit the Boc deprotection reaction to occur. The reaction is monitored by HPLC or reverse
5 phase TLC. When complete, agitation is discontinued and the phases are allowed to separate. The lower, organic phase is removed and set aside. The reactor is then charged with 12.7 Kg (9.6 L) of dichloromethane as an extraction solvent, the mixture is agitated, phases are allowed to separate, and the organic dichloromethane phase is removed. The organic extracts are combined and discarded. The remaining aqueous phase is diluted with 18.3 Kg distilled water and the
10 temperature is raised to approximately 50°C. Distillation under vacuum (100-400 torr) is performed to remove residual dichloromethane from the reaction. The pH of the reaction is then adjusted to between 7.8-8.1 using about 9.42 Kg of 3.0N NaOH (aq) solution while keeping the temperature of the reaction below 65°C. The reaction is cooled to 50°C and the precipitated solids are aged for at least an hour prior to cooling the mixture to room temperature. The solids
15 are isolated by suction filtration and washed twice with 5.2 Kg portions of distilled water. The solids are dried for at least 12 hours with suction and then for an additional 12 hours in a convection oven at 55°C. The yield achieved for intermediate (23) in this example is 3.2 Kg (79%). A reactor is charged with 3.2 Kg solid intermediate (23) and the solids are suspended in 25.6 Kg of 95% ethanol as solvent. To the reactor is then added 1.1 Kg of solid D,L-malic acid
20 (24), and the mixture is heated to reflux temperature (~80°C). Distilled water (~5.7 L) is added to the reaction until a complete solution is achieved and 0.2 Kg of activated charcoal is added. The reaction mixture is passed through a filter to achieve clarification, cooled to 45°C and held for a period of at least 2 hours to allow crystallization to occur. The reaction mixture is further cooled to 5°C and the suspended solids are isolated by suction filtration. The solids are then
25 washed with 6.6 KG of 95% ethanol and dried for at least 4 hours with suction under vacuum. The solids are then further dried in a convection oven for at least 12 hours at 45°C to afford 3.1 Kg of intermediate (24) (70%). NMR (D₂O, 300 MHz) δ (ppm): 8.54 (s, 1H), 7.37 (d, J =9.0 Hz, 1H), 7.05 (d, J =9.0 Hz, 1H), 4.23-4.18 (m, 1H), 4.10-3.89 (m, 1H), 3.66 (br s, 1H), 3.58 (s, 3H), 3.45 (d, J =9.0 Hz, 1H), 3.34 (d, J =9.3 Hz, 1H), 3.16 (d, J =12.9 Hz, 1H), 2.65 (dd, J =16.1, 4.1 Hz, 1H), 2.64-2.53 (m, 1H), 2.46 (dd, J =16.1, 8.0 Hz, 1H), 2.06 (br s, 1H), 1.87 (d, J =14.4 Hz, 1H), 1.58-1.45 (m, 1H), 1.15-0.95 (m, 2H), 0.91 (d, J =6.3 Hz, 3H), 0.85-0.78 (m, 2H). TLC (Whatman MKC18F Silica, 60Å, 200 μ m), Mobile Phase: 1:1 (v/v) CH₃CN : 0.5N NaCl (aq),

UV (254/366 nm) visualization. HPLC: Mobile Phase H₂O with 0.1% formic acid/Acetonitrile with 0.1% formic acid, gradient elution with 88% H₂O/formic acid to 20% H₂O/formic acid, Zorbax SB-C8 4.6mm x 150 mm column, Part No. 883975.906, 1.5 ml/min rate, 20 min run time, 292 nm, Detector Model G1314A, S/N JP72003849, Quat Pump Model G1311A, S/N
5 US72102299, Auto Sampler Model G1313A, S/N DE14918139, Degasser Model G1322A, S/N JP73007229; approximate retention time for intermediate (19): 13.0 min; approximate retention time for intermediate (20): 11.6 min; approximate retention time for intermediate (21): 16.3 min; approximate retention time for intermediate (22): 18.2 min; approximate retention time for intermediate (23): 8.6 min; approximate retention time for compound (25): 8.6 min.

10

Except as otherwise noted, all amounts including quantities, percentages, portions, and proportions, are understood to be modified by the word "about", and amounts are not intended to indicate significant digits.

Except as otherwise noted, the articles "a", "an", and "the" mean "one or more".

15

All documents cited in the Detailed Description of the Invention are, in relevant part, incorporated herein by reference; the citation of any document is not to be construed as an admission that it is prior art with respect to the present invention. To the extent that any meaning or definition of a term in this written document conflicts with any meaning or definition of the term in a document incorporated by reference, the meaning or definition assigned to the
20 term in this written document shall govern.

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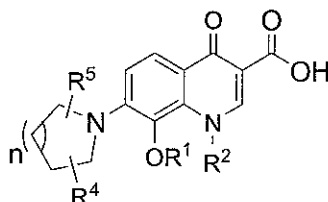
While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications may be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are
25 within the scope of this invention.

25

CLAIMS

What is claimed is:

1. A process for preparing a substituted quinolone according to Formula I:



Formula I

wherein:

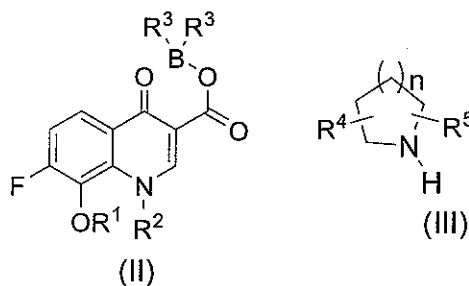
R¹ is C₁-C₄ alkyl;

R² is C₁-C₄ alkyl or C₃-C₆ cycloalkyl;

R⁴ and R⁵ are each independently selected from a group consisting of amino, C₁-C₄ alkylamino, protected amino, and C₁-C₄ alkyl; and

n is 1 or 2;

said process comprising: the step of reacting a compound of Formula II with compound of Formula III in the presence of a suitable base at about 20°C to about 80°C, followed by hydrolysis:

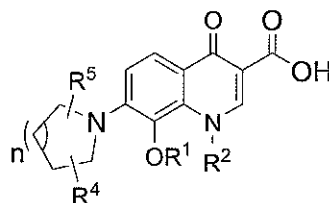


wherein:

R³ is acetoxy; and

R¹, R², R⁴, R⁵, and n are as defined for Formula I above.

2. A process for preparing a substituted quinolone according to Formula I:



Formula I

wherein:

R¹ is C₁-C₄ alkyl;

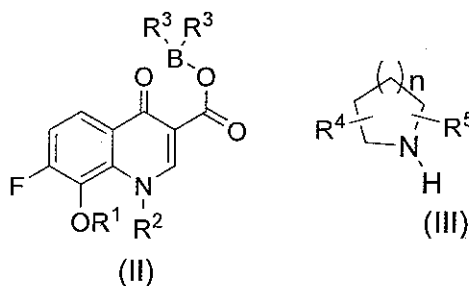
R² is C₁-C₄ alkyl or C₃-C₆ cycloalkyl;

R⁴ is selected from a group consisting of amino, C₁-C₄ alkylamino, protected amino, and C₁-C₄ alkyl;

R⁵ is amino-tert-butoxycarbonyl; and

n is 1 or 2;

said process comprising: the step of reacting a compound of Formula II with compound of Formula III in the presence of a suitable base at about 20°C to about 80°C, followed by hydrolysis:

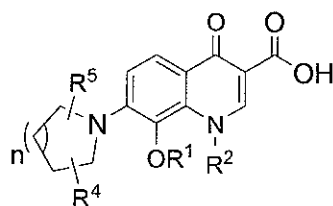


wherein:

R³ is unsubstituted or substituted C₁-C₄ acyloxy; and

R¹, R², R⁴, R⁵, and n are as defined for Formula I above.

3. A process according to claim 2, wherein the resulting compound of Formula I is subsequently subjected to a process of deprotecting the amino group of R⁵.
4. A process for preparing a substituted quinolone according to Formula I:



Formula I

wherein:

R¹ is C₁-C₄ alkyl;

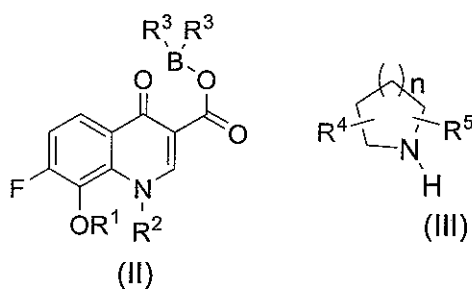
R² is C₁-C₄ alkyl or C₃-C₆ cycloalkyl;

R⁴ is methyl;

R⁵ is amino-tert-butoxycarbonyl; and

n is 2;

said process comprising: the step of reacting a compound of Formula II with compound of Formula III in the presence of a suitable base at about 20°C to about 80°C, followed by hydrolysis:

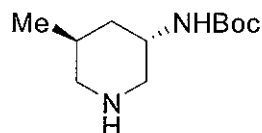


wherein:

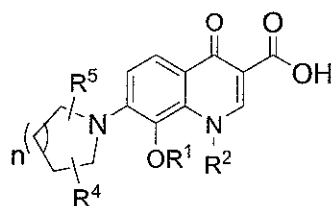
R³ is unsubstituted or substituted C₁-C₄ acyloxy; and

R¹ and R² are as defined for Formula I above; and

the compound of Formula III is:



5. A process for preparing a substituted quinolone according to Formula I:



Formula I

wherein:

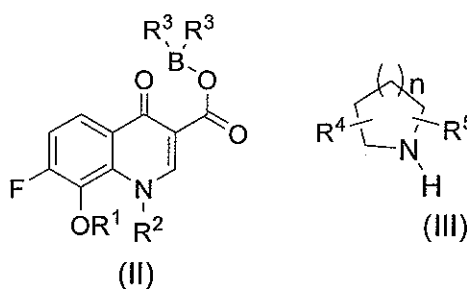
R¹ is C₁-C₄ alkyl;

R² is C₁-C₄ alkyl or C₃-C₆ cycloalkyl;

R⁴ and R⁵ are each independently selected from a group consisting of amino, C₁-C₄ alkylamino, protected amino, and C₁-C₄ alkyl; and

n is 1 or 2;

said process comprising: the step of reacting a compound of Formula II with compound of Formula III in the presence of a suitable base at 20°C to 80°C, followed by hydrolysis:



wherein:

the base is selected from the group consisting of triethylamine, diisopropylethylamine, triisopropyl amine, and 1,8-diazabicyclo[5.4.0]undec-7-ene;

R³ is unsubstituted or substituted C₁-C₄ acyloxy; and

R¹, R², R⁴, R⁵, and n are as defined for Formula I above.

6. A process according to claim 5, wherein the base is triethylamine.