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Clarke, Modet & C^o

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 05-003900-00013-0000

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Act: 44 RESPUESTA/REQE Folio: 27

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. S. D.

Re: Expediente No. **05-003.900**

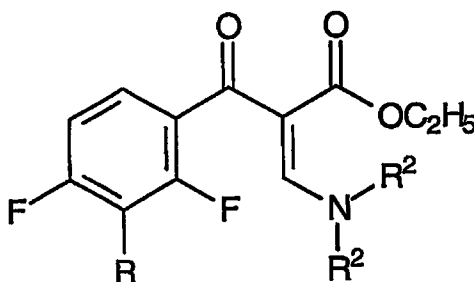
Solicitud de patente a nombre de **THE PROCTER & GAMBLE COMPANY.**

Yo, DILIA MARIA RODRIGUEZ D'ALEMAN, actuando como apoderada sustituta de acuerdo con la sustitución presentada el 29 de diciembre de 2009, identificada como aparece al pie de mi firma, domiciliada en la carrera 11 A No. 86-53, piso 6, obrando como apoderada de la sociedad **THE PROCTER & GAMBLE COMPANY**, domiciliada en Ohio, Estados Unidos de América, solicitante de la patente de la referencia, en respuesta al oficio No. 05520 notificado por fijación en 30 de abril de 2010 relacionado con el concepto técnico de fondo No. 1332, me permito manifestar lo siguiente:

1. Con fundamento en la facultad que confiere el artículo 34 de la Decisión 486 al solicitante para modificar la solicitud de patente en cualquier momento del trámite, presento junto con este memorial nuevo juego de reivindicaciones, que ahora consta de 25 cláusulas, en el cual se realizan las siguientes modificaciones:

1.1 S corrigió la fórmula de la reivindicación 11 con el fin de que el grupo sea etoxilo y no metoxilo.

1.2 Se introdujo en la reivindicación 1 la fórmula



En relación con estas modificaciones, nos permitimos manifestar que las mismas no amplían en ningún sentido el alcance de la solicitud como fue originalmente

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presentada y se realizan con el fin atender las observaciones hechas por el señor examinador.

Teniendo en cuenta el concepto técnico emitido por el Señor Superintendente Delegado para la propiedad intelectual GianCarlo Marcenaro Jiménez a la doctora Ana Maria Castro Wey, que da alcance a las comunicaciones No. 09-001524 y 09-012566, no se presenta una tasa adicional, toda vez la solicitud fue presentada con anterioridad al 1 de enero de 2009.

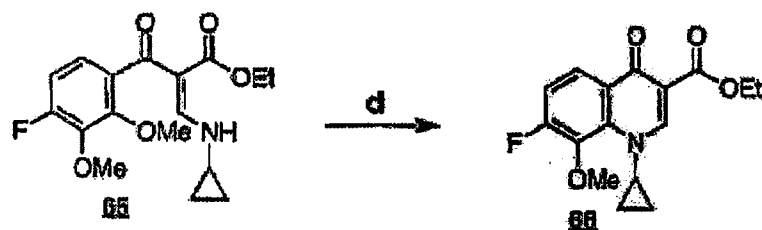
2. Claridad de la Solicitud

En cuanto a la observación del señor examinador relacionada con incluir la reivindicación 1 como una etapa del proceso de la reivindicación 11, respetuosamente nos permitimos decir que el solicitante no se encuentra de acuerdo con esta limitación, toda vez que la reivindicación 1 y 11 tienen alcances diferentes. De hecho, la reivindicación 1 es la forma más sencilla del proceso y la reivindicación 11 es la forma más compleja del mismo. Por consiguiente, el inventor solicita comedidamente sea retirada esta objeción.

De otra parte, en cuanto a la objeción de la presencia del éster metílico en lugar del éster etílico, nos permitimos decir que se corrigió la fórmula de acuerdo con lo manifestado en la página 10 y 11 de la descripción.

3. Novedad

El señor examinador establece en su concepto técnico que “el documento D1 (ejemplo 5, página 88) describe un procesos para obtener una quinolona (66) mediante la ciclación del correspondiente intermedio (65) de acuerdo al siguiente esquema y condiciones de la etapa d:



Etapla d: El producto 4 es disuelto en acetonitrilo anhidro (150 mL), se adiciona N,O-bis(trimetilsilil)acetaminda (115g). La solución se agita a temperatura ambiente durante 0,5 horas y se calienta a reflujo.”

Sobre este particular, nuevamente y de manera respetuosa nos permitimos decir que el artículo 16 de la Decisión 486 establece que: “Una invención se considera nueva cuando no está comprendida en el estado de la técnica”

El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida....”(el resaltado es nuestro).

Si de acuerdo con el espíritu de la norma legal indicada, la invención no se considera como nueva si está “comprendida” en el estado de la técnica, dicha norma se está refiriendo, naturalmente, a la totalidad del invento y no a alguno o a algunos de los componentes que hacen parte de la nueva solicitud.

En efecto, para que la invención pierda su calidad de novedosa, es claro que ella, TODA ELLA, ha de estar contenida en el “*conjunto de conocimientos existentes que son aplicables al proceso industrial*” como define el estado de la técnica el Tribunal de justicia del Acuerdo de Cartagena (Proceso No. 6-IP-89, sentencia de 31 de octubre de 1989, publicada en Jurisprudencia del Tribunal de Justicia del Acuerdo de Cartagena, Tomo 11, BID-INTAL, Buenos Aires, 1994, página 60).

Lo anterior se conoce como NOVEDAD ABSOLUTA, de conformidad con lo cual para desvirtuar el requisito de novedad de una invención será necesario que lo reivindicado por la invención bajo estudio corresponda de forma total con lo revelado en un documento o anterioridad señalada, conclusión a la que se llega después de un análisis exhaustivo mediante una comparación entre el capítulo reivindicatorio de la invención en estudio y la divulgación citada por ese despacho como anterioridad.

Ahora bien, si un determinado elemento, condición o circunstancia de la nueva creación ya hace parte del estado de la técnica no quiere ello decir, desde luego, que la invención deba ser rechazada por carecer del requisito de novedad. No sin razón ha dicho el mencionado Tribunal: “*hay que advertir que toda creación es en cierta forma, producto del estado de la técnica existente, en el sentido de que el inventor ha de tener en cuenta un conjunto de conocimientos técnicos que le permitan crear nuevos procedimientos aplicables a la industria*” (Ibidem, páginas 53 y 54) (El subrayado es nuestro).

Por lo tanto y teniendo en cuenta lo anteriormente expuesto, como mínimo la novedad debe contemplar los siguientes aspectos:

-Que la invención en estudio esté contenida de forma TOTAL y ABSOLUTA en el documento que se menciona como anterioridad; y

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-Que la invención en cuestión puede partir de conocimientos conocidos, caso en el cual habrá que hacer la comparación no de lo conocido sino de lo inédito y novedoso, teniendo que analizarse el valor agregado que aporta la invención con sus nuevas características al campo técnico al cual pertenece la solicitud en estudio.

Aplicando lo anterior al caso concreto, para que las razones que aduce ese despacho para desvirtuar la novedad fuesen ciertas, sería forzoso que se demostrara que la invención de mi mandante está comprendida en el estado de la técnica de forma **TOTAL**, lo cual no sucede debido a que la presente invención requiere de dos precursores específicos de quinolona, es decir, tanto aquel que tiene el grupo etoxilo en la posición 2 del grupo fenílico como el precursor que tiene un átomo de flúor en la posición 2 del grupo fenilo. En clara diferencia, D1 tan solo reporta que la ciclización se realiza sobre el compuesto que tiene el grupo etoxilo en la posición 2 del grupo fenilo.

De acuerdo con lo anterior, respetuosamente nos permitimos decir que el nuevo capítulo reivindicatorio es novedoso sobre lo mostrado en D1 ya que requiere la presencia de los dos precursores específicos de quinolona.

4. Nivel inventivo

En cuanto a este requisito, el señor examinador indica que no existiría un efecto sorprendente en lograr ciclizar el derivado de flúor en la posición 2 del anillo fenílico por ser éste derivado también sometido a las mismas condiciones de ciclización que el compuesto 2-etoxilado.

En este sentido, respetuosamente dirigimos la atención del señor examinador a las páginas 9 a 11 de la memoria descriptiva donde se pone de manifiesto que existía un problema en el estado del arte relacionado con la eliminación indeseada del átomo de flúor en la posición 2 durante la preparación de los precursores de antibióticos de quinolona, donde dicho átomo de flúor era sustituido por un grupo etoxilo, lo cual disminuía el rendimiento de la reacción principal.

En este sentido, el solicitante encontró que de manera sorprendente se puede realizar la ciclización de dicho subproducto etoxilado en la segunda posición del anillo fenílico mediante una reacción con el aducto de 2-fluoro correspondiente en una reacción llevada en condiciones suaves y de alto rendimiento. Por lo tanto, resulta inesperado que el compuesto 2-etoxilado, que es un subproducto de la primera reacción, pueda ser también ciclizado de manera exitosa junto con el compuesto de interés, es decir, con el compuesto 2-fluoro, sin que exista entonces la necesidad de una purificación intermedia.

Por su parte, el documento D1 no revela ni sugiere la presencia de este segundo producto, nos permitimos manifestar que una persona medianamente versada en la técnica no habría encontrado motivación alguna a partir de lo mostrado en D2 para solucionar las deficiencias señaladas anteriormente en D1, pues D1 claramente parte de un compuesto derivado de ácido benzóico que tiene en su posición 2 un grupo metoxilo y para nada menciona o sugiere que sea importante tener derivados de estos compuestos con un átomo de flúor en dicha posición.

En este sentido, D2 tampoco hace ningún reporte o sugerencia relacionado con la posición 2 del grupo fenílico. Aún más, D2 tampoco hace ningún reporte en cuanto a la afectación del rendimiento en la producción de compuestos intermediarios de quinolona. En D2, como se puede apreciar en su descripción, el primer paso del ejemplo 9, el grupo flúor en la posición 4 del anillo fenílico es reemplazado por un anillo 4-metilpiperazina, el cual está claramente en contraposición al proceso reclamado en la presente solicitud, especialmente mostrado en la cláusula 11, donde el grupo flúor en la posición 4 se encuentra presente a lo largo de toda la reacción.

Así las cosas, los reactivos mostrados y enseñados en D2 son completamente diferentes de aquellos señalados en la nueva reivindicación 11. Por consiguiente, los pasos de reacción también son diferentes y la reacción reclamada, por ende, es inventiva sobre lo mostrado en D1 y D2. Aún más, El solicitante encontró de manera sorprendente que el compuesto 2-etoxi, el cual fue un subproducto inesperado en el primer paso de la reacción, también puede ser exitosamente ciclizado junto con el compuesto de interés (compuesto 2-fluoro) sin la necesidad de una purificación intermedia, produciendo los intermediarios antibióticos de quinolona con un alto rendimiento y con condiciones más suaves que las mostradas en los documentos citados donde por ejemplo se emplean atmósferas de nitrógeno, caso de D2 ejemplo 1.

En consecuencia, respetuosamente manifestamos que ninguna de las anterioridades D1 y D2 reporta o sugiere realizar la ciclización de una mezcla de los compuestos 2-fluoro y 2-etoxi en el grupo fenílico para producir los intermediarios antibióticos de quinolona de la presente invención.

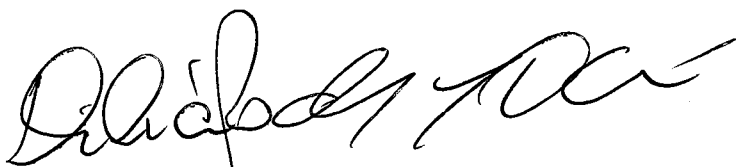
Sumado a lo anterior, una persona medianamente versada en la técnica no habría encontrado ningún tipo de información útil en D1 y D2 que le hubiera permitido derivar de manera evidente el resultado de la ciclización de ambas especies con alto rendimiento para llegar al producto deseado a partir de lo mostrado en D1 y D2, pues ninguna de estas referencias se enfoca en el problema del rendimiento de la reacción y su posible afectación por la presencia de un sub-producto como lo es el compuesto fenílico con su posición 2 etoxilada.

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Finalmente, nos permitimos manifestar que aunque sabemos de la independencia entre las oficinas de propiedad intelectual, es deseo del solicitante informar que el juego de reivindicaciones que se presenta con este memorial corresponde a las reivindicaciones que fueron concedidas para la correspondiente solicitud Estadounidense **US 6,803,469 B2**, de la cual nos permitimos anexar una copia informal.

Habiendo atendido cabalmente las objeciones presentadas por ese despacho, atentamente solicitamos se conceda el privilegio de patente de invención a la solicitud en estudio o si el examinador considera que subsisten razones para objetar la presente invención, rogamos expedir otro examen de fondo con los debidos motivos y razones que sustenten su objeción con el fin de que nuestro mandante tenga la posibilidad de exponer sus argumentos con base en la interpretación de los artículos 45 de la Decisión 486 -el cual otorga la facultad al examinador para emitir los exámenes de fondo-, 35 y 59 del Código Contencioso Administrativo que señala que: *"habiéndose dado oportunidad a los interesados para expresar sus opiniones, y con base en las pruebas e informes disponibles, se tomará la decisión que será motivada al menos en forma sumaria si afecta a particulares"* y *"(..) deberá proferirse la decisión definitiva. Esta se motivará en sus aspectos de hecho y de derecho, y en los de conveniencia si es el caso"*, respectivamente (El subrayado es nuestro).

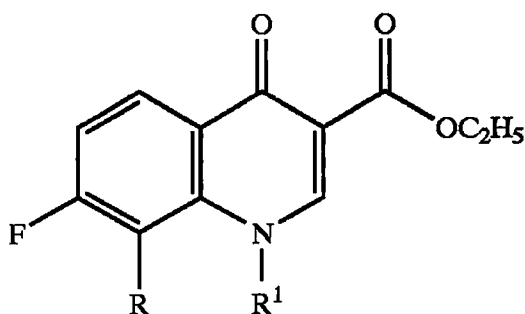
En consecuencia, pedimos a ese despacho pronunciarse en relación con todos los argumentos presentados en este memorial dando estricta aplicación al principio del debido proceso consagrado en el artículo 29 de la Constitución Nacional



DILIA MARÍA RODRÍGUEZ D'ALEMAN
C.C. 41.654.882 de Bogotá.
T.P. 20824 CSJ

REIVINDICACIONES

1. Un proceso para preparar un intermedio de
5 antibiótico de quinolona que tiene la fórmula:

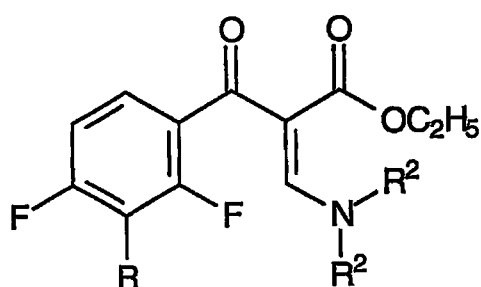
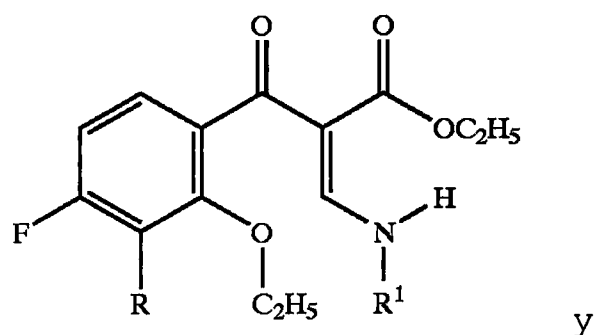


caracterizado porque R es alquilo de 1 a 2 átomos de
carbono, fluoroalquilo de 1 a 2 átomos de carbono,
alquenilo de 2 a 4 átomos de carbono, metoxi, cloro
10 o bromo;

R¹ es una unidad escogida del grupo formado por
alquilo de 1 a 2 átomos de carbono, alquenilo de 2 a
3 átomos de carbono, cicloalquilo de 3 a 5 átomos de
carbono y fenilo, cada una de las cuales puede ser
15 sustituida por uno o más átomos de flúor; el proceso
comprende el paso de ciclizar una mezcla de
precursores de quinolona; la mezcla comprende un
intermedio de 2-etoxi sustituido que tiene la
fórmula:

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en presencia de un agente de sililación.

2. Un proceso según la reivindicación 1, caracterizado porque R es -OCH₃.

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3. Un proceso según la reivindicación 1, caracterizado porque R es -CH₃, -CH₂F, -CHF₂ y -CF₃.

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4. Un proceso según la reivindicación 1, caracterizado porque R es -Cl.

5. Un proceso según la reivindicación 1, caracterizado porque R es -CH₂CH=CH₂.

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6. Un proceso de conformidad con la reivindicación 1, caracterizado porque la ciclización se realiza en

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presencia de un solvente seleccionado del grupo formado por cloruro de metileno, diclorometano, hexametilfosforamida, tetrahidrofurano, benceno, tolueno, alcanos y mezclas de éstos.

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7. Un proceso de conformidad con la reivindicación 1, caracterizado además porque el agente de sililación se selecciona del grupo formado por clorotrimetilsilano, N,O-

10 bis(trimetilsilil)acetamida, N,O-

bis(trimetilsilil)trifluoroacetamida,

bis(trimetilsilil)urea, hexametiltrisilazano, N-

metil-N-trimetilsililtrifluoroacetamida, 1-

trimetilsilil-imidazol, trimetilsilil

15 trifluormetanosulfonato, ter-

butildimetilclorosilano, 1-(ter-

butildimetilsilil)imidazol, N-ter-butildimetil-N-

metiltrifluoroacetamida, ter-

butildimetilsililtrifluorometanosulfonato, ter-

20 butilfenilclorosilano, ter-butyl-

metoxifenilbromosilano, dimetilfenilclorosilano,

triethylclorosilano, trimetilsilil

trifluorometanosulfonato y trifenilclorosilano.

25 8. Un proceso de conformidad con la reivindicación 7, caracterizado porque el agente de sililación es N,O-bis(trimetilsilil)acetamida.

9. Un proceso de conformidad con la reivindicación

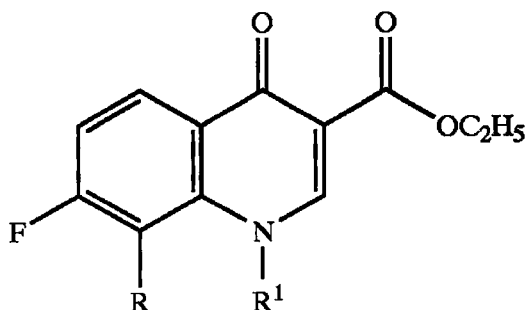
30 1, caracterizado porque R¹ ciclopropilo, metilo, etilo y bencilo.

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10. Un proceso de conformidad con la reivindicación 1, caracterizado porque la ciclización se realiza mediante reflujo en presencia de un solvente.

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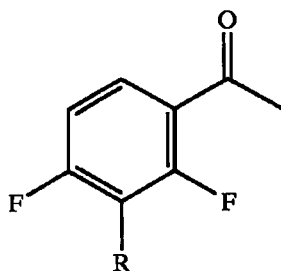
11. Un proceso para preparar un intermedio de antibiótico de quinolona que tienen la fórmula:



10 caracterizado porque R es alquilo de 1 a 2 átomos de carbono, fluoroalquilo de 1 a 2 átomos de carbono, alquenilo de 2 a 4 átomos de carbono, metoxi, cloro o bromo;

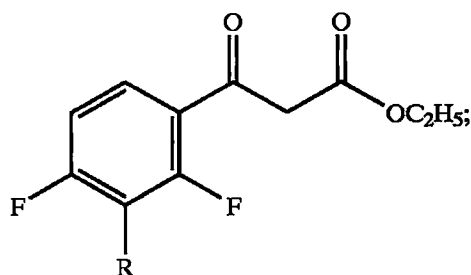
15 R¹ es una unidad escogida del grupo formado por alquilo de 1 a 2 átomos de carbono, alquenilo de 2 a 3 átomos de carbono, cicloalquilo de 3 a 5 átomos de carbono y fenilo, cada una de las cuales puede ser sustituida por uno o más átomos de flúor; este proceso comprende los pasos de:

20 a) Reaccionar una acetofenona que tienen la fórmula

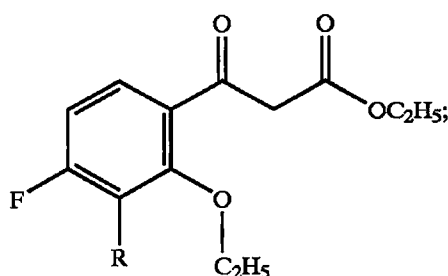


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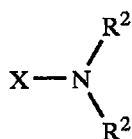
con carbonato de dietilo en presencia de una base para formar una mezcla de 4-fluoro β -cetoésteres que tienen la fórmula:



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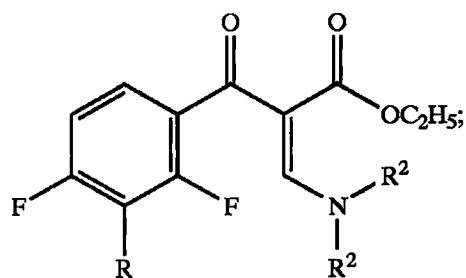
b) reaccionar dicha mezcla de un aducto de la reacción Knoevenagel que tienen la fórmula:



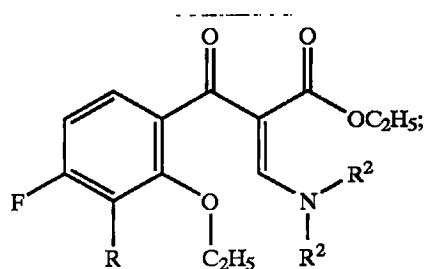
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en donde R^2 es alquilo de 1 a 4 átomos de carbono lineal o ramificado, fenilo y mezclas de éstos; X es una unidad de aldehído o un equivalente de una unidad de aldehído; para formar una mezcla de intermedios de imina que tiene la fórmula:

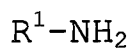
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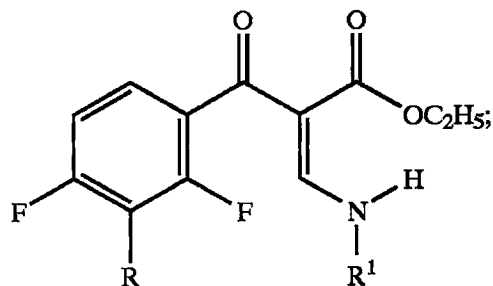
y



- 5 c) reaccionar la mezcla de intermedios de imina con una mezcla que tiene la fórmula

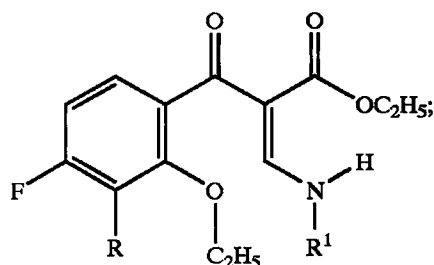


- 10 para formar una mezcla de intermedios de quinolona que tienen la fórmula

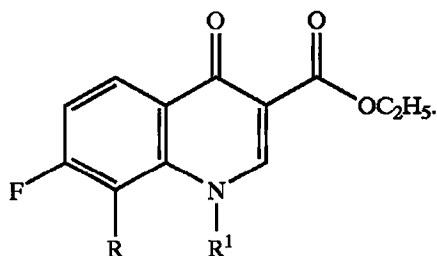


y

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- d) ciclizar la mezcla de intermedios de quinolina en presencia de un agente de sililación para formar el intermedio de antibiótico de quinolina que tiene la fórmula:



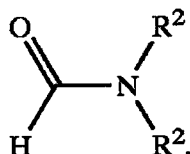
12. Un proceso según la reivindicación 11, caracterizado porque la base en el paso (a) es un hidruro metálico seleccionado del grupo LiH, NaH, KH, CaH₂ y mezclas de éstos.
13. Un proceso según la reivindicación 11, caracterizado porque la base en el paso (a) es una base inorgánica escogida del grupo Na₂CO₃, NaHCO₃, K₂CO y mezclas de éstos
14. Un proceso según la reivindicación 11, caracterizado porque la base en el paso (a) es una base orgánica escogida de butil litio y diisopropilamida de litio.

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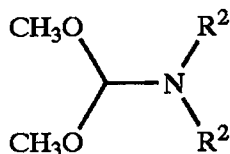
15. Un proceso de conformidad con la reivindicación 11, caracterizado porque el paso (a) comprende reaccionar un mol de un sustituido acetofenona con 2,2 moles de una base y 2,4 moles de carbonato de dietilo.

16. Un proceso de conformidad con la reivindicación 11, caracterizado porque el paso (a) se realiza en presencia de un solvente seleccionado del grupo formado por cloruro de metileno, dicloro-metano, hexametilfosforamida, tetrahidrofurano, benceno, tolueno, alcanos y mezclas de éstos.

17. Un proceso de conformidad con la reivindicación
15 11, caracterizado además porque el aducto es un
aldehído que tiene la fórmula:



18. Un proceso de conformidad con la reivindicación
20 11, caracterizado además porque el aducto es un
dimetilacetal que tiene la fórmula:



caracterizado además porque R² es metilo, etilo y mezclas de éstos.

19. Un proceso de conformidad con la reivindicación

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11, caracterizado porque el paso (b) se realiza en presencia de tolueno, caracterizado además porque el aducto es un dimetilacetal y caracterizado además porque la mezcla obtenida del paso (a) y el
5 dimetilacetal se calienta para eliminar azeotrópicamente cualquier metanol que se haya formado.

20. Un proceso de conformidad con la reivindicación 11, caracterizado porque la amina primaria en el paso (c) es escoge del grupo formado por metilamina, etilamina y ciclopropilamina.

21. Un proceso de conformidad con la reivindicación 11, caracterizado porque el paso (c) se realiza en presencia de un solvente seleccionado del grupo formado por cloruro de metileno, dicloro-metano, hexametilfosforamida, tetrahidrofurano, benceno, tolueno, aléanos y mezclas de éstos.

22. Un proceso de conformidad con la reivindicación 11, caracterizado porque el paso (d) se realiza en presencia de un solvente seleccionado del grupo formado por cloruro de metileno, diclorometano, hexametilfosforamida, tetrahidrofurano, benceno,
25 tolueno, alcanos y mezclas de éstos.

23. Un proceso de conformidad con la reivindicación 11, caracterizado además porque el agente de sililación se selecciona del grupo formado por
30 clorotrimetilsilano, N,O-

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bis(trimetilsilil)acetamida, N,O-
bis(trimetilsilil)trifluoroacetamida,
bis(trimetilsilil)urea, hexametiltrisilazano, N-
metil-N-trimetilsililtrifluoroacetamida, 1-
5 trimetilsilil-imidazol, trimetilsilil
trifluorometanosulfonato, ter-
butildimetilclorosilano, 1-(ter-
butildimetilsilil)imidazol, N-ter-butildimetil-N-
metiltrifluoroacetamida, ter-
10 butildimetilsililtrifluorometano sulfonato, ter-
butilfenilclorosilano, ter-butyl-
metoxifenilbromosilano, dimetilfenilclorosilano,
triethylclorosilano, trimetilsilil
trifluorometanosulfonato y trifenilclorosilano.

15

24. Un proceso según la reivindicación 23
caracterizado porque el agente de sililación es N,O-
bis(trimetilsilil)acetamida.

20 25. Un proceso según la reivindicación 11,
caracterizado porque el paso (d) se lleva a cabo
mediante reflujo en presencia de un solvente.

16



US006803469B2

(12) **United States Patent**
Randall

(10) **Patent No.:** **US 6,803,469 B2**
(45) **Date of Patent:** **Oct. 12, 2004**

(54) **PROCESS FOR PREPARING QUINOLONE
ANTIBIOTIC INTERMEDIATES**

(75) **Inventor:** **Jared Lynn Randall, Smyrna, NY (US)**

(73) **Assignee:** **The Procter & Gamble Company,
Cincinnati, OH (US)**

(*) **Notice:** Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 0 days.

(21) **Appl. No.:** **10/630,608**

(22) **Filed:** **Jul. 30, 2003**

(65) **Prior Publication Data**

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Related U.S. Application Data

(60) **Provisional application No. 60/401,184, filed on Aug. 5,
2002.**

(51) **Int. Cl.⁷** **C07D 215/56**

(52) **U.S. Cl.** **546/196**

(58) **Field of Search** **546/196**

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,695,646 A * 9/1987 Maurer et al. 560/43
5,703,231 A 12/1997 Randall et al.

FOREIGN PATENT DOCUMENTS

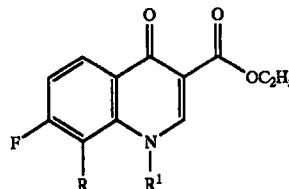
WO WO 96/04247 2/1996
WO WO 96/04286 2/1996
WO WO 02/48113 6/2002

* cited by examiner

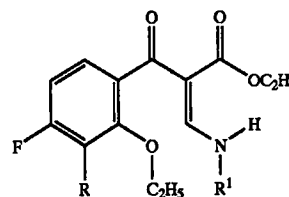
Primary Examiner—Bernard Dentz
(74) *Attorney, Agent, or Firm*—Richard S. Echler, Sr.

(57) **ABSTRACT**

The present invention relates to a process for preparing a
quinolone antibiotic intermediate having the formula:



wherein R is C₁–C₂ alkyl, C₁–C₂ fluoroalkyl, C₂–C₄
alkenyl, methoxy, chloro, or bromo; R¹ is a unit selected
from the group consisting of C₁–C₂ alkyl, C₂–C₃ alkenyl,
C₃–C₅ cycloalkyl, and phenyl, each of which can be sub-
stituted by one or more fluorine atoms; said process com-
prising the step of cyclizing an admixture of quinolone
precursors, said admixture comprising a 2-ethoxy substi-
tuted intermediate having the formula:



in the presence of a silylating agent.

25 Claims, No Drawings

752
149

17

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PROCESS FOR PREPARING QUINOLONE ANTIBIOTIC INTERMEDIATES

CROSS REFERENCE TO RELATED APPLICATION

This application claims priority under Title 35, United States Code 119(e) from Provisional Application Ser. No. 60/401,184, filed Aug. 5, 2002.

FIELD OF THE INVENTION

The present invention relates to a process for preparing quinolone antibiotic intermediates. The process of the present invention utilizes the surprising result that 3-(2-alkoxyphenyl)-2-enamine-3-oxo-propionic acid ester by-products can be carried forward and are suitable intermediates for the final quinolone products.

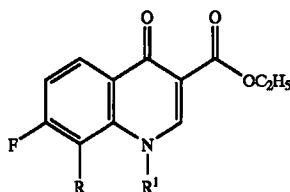
BACKGROUND OF THE INVENTION

Quinolone and quinolonyl antibiotics are a recent class of highly potent, broad spectrum antimicrobials and research has been directed at developing this new class of antimicrobials, especially those effective against Gram positive pathogens, inter alia, vancomycin-resistant *Enterococcus faecium*. These quinolone and quinolonyl antibiotics and their preparation are well described in the documents cited herein below.

However, some categories of quinolone antibiotic analogs have substituents along the quinolone ring system which render the synthesis of these analogs cumbersome, indirect, and only achievable in low overall yield. There is therefore a long felt need for a process for making the quinolone and quinolonyl antibiotic intermediates described herein, said process encompassing a direct, high yield, low cost series of reactions thereby benefiting the consumer with effective, affordable antibiotics.

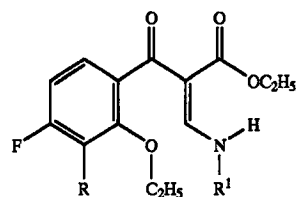
SUMMARY OF THE INVENTION

The present invention relates to the surprising discovery that quinolone antibiotic intermediates having the formula:

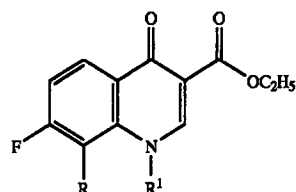


wherein R is C₁-C₂ alkyl, C₁-C₂ fluoroalkyl, C₂-C₄ alkenyl, methoxy, chloro, or bromo; R¹ is a unit selected from the group consisting of C₁-C₂ alkyl, C₂-C₃ alkenyl, C₃-C₅ cycloalkyl, and phenyl, each of which can be substituted by one or more fluorine atoms; can be prepared by reacting an admixture of quinolone antibiotic intermediate precursors, said admixture comprising a 2-ethoxy substituted intermediate having the formula:

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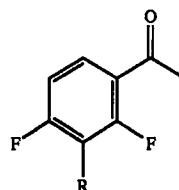


with a silylating agent as a ring closure reaction catalyst. In general the present invention relates to a process for preparing quinolone antibiotic intermediates having the formula:

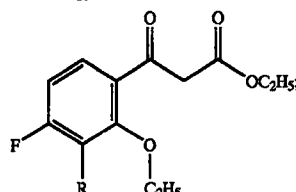
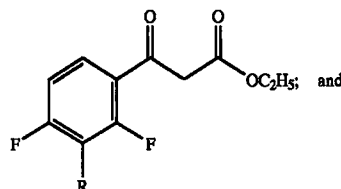


wherein R and R¹ are defined herein; said process comprising the steps of:

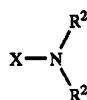
a) reacting an acetophenone having the formula:



with diethylcarbonate in the presence of a base to form an admixture of 4-fluoro β-ketoesters having the formula:



b) reacting said admixture with an amine capable of undergoing a Knoevenagel Reaction, said amine having the formula:

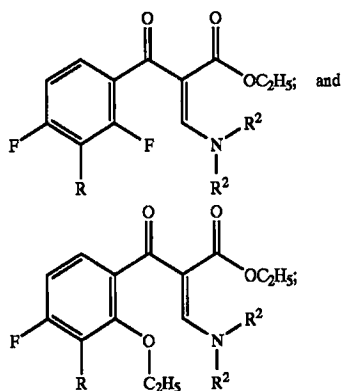


wherein R² is C₁-C₄ linear or branched alkyl, phenyl, and mixtures thereof; X is an aldehyde unit or an aldehyde

153
150

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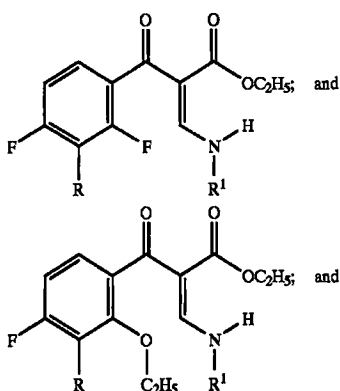
unit equivalent; to form an admixture of enamine intermediates having the formula:



c) reacting said enamine intermediate admixture with an amine having the formula:

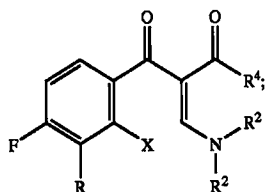


to form an admixture of quinolone intermediates having the formula:



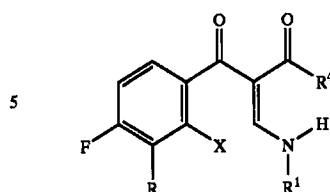
d) cyclizing said quinolone intermediate admixture in the presence of a silylating agent to form the quinolone antibiotic intermediates according to the present invention.

The present invention further relates to novel compounds having the formula:



and the formula:

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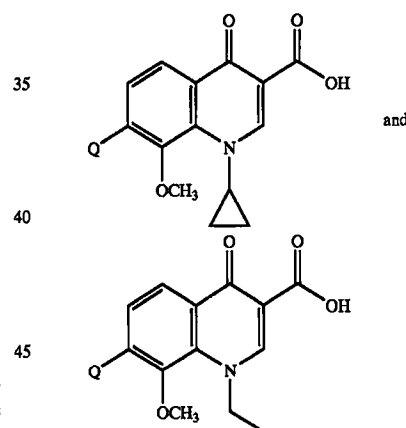


wherein R, R¹, and R⁴ are defined herein above, X is a suitable leaving group, said compounds suitable for use as intermediates in the preparation of quinolone antibiotics according to the present invention.

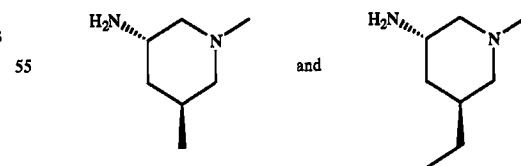
These and other objects, features, and advantages will become apparent to those of ordinary skill in the art from a reading of the following detailed description and the appended claims. All percentages, ratios and proportions herein are by weight, unless otherwise specified. All temperatures are in degrees Celsius (° C.) unless otherwise specified. All documents cited 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.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to the surprising discovery that 1-lower alkyl-8-substituted quinolones, inter alia, 1-cyclopropyl and 1-ethyl-8-methoxyquinolone carboxylic acids of the formula:



wherein Q is an amino-substituted pyrrolidine or piperidine, inter alia, units having the formula:

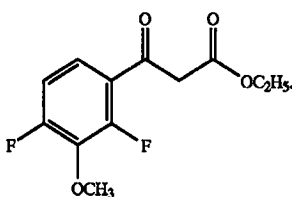


display high levels of efficacy toward Gram positive bacteria.

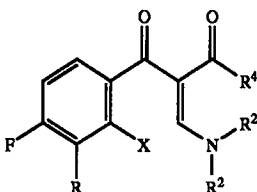
As a result of this surprising discovery, there developed a long felt need for a high yield, low cost convergent synthesis for antibiotics of this compound class. In addition, there developed a desire for a process adaptable to the broadest range of analogs comprising this class of antibiotics.

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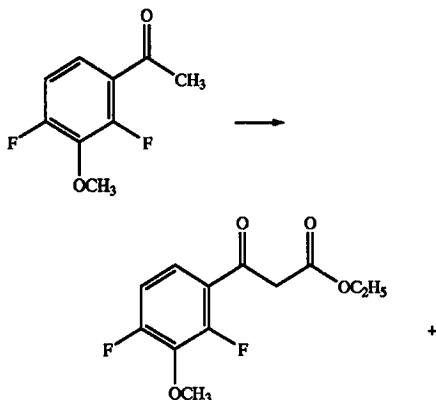
Our investigation of quinolone antibiotics of this category is well disclosed in U.S. Pat. No. 6,329,391 B1 Ledoussal et al., issued Dec. 11, 2001 and U.S. Pat. No. 6,387,928 B1 Ledoussal et al., issued May 14, 2002, both of which are incorporated herein by reference. The process described therein involved reaction conditions and procedures which protected against the unwanted elimination of the 2-position fluorine atom during the preparation of quinolone antibiotic precursors, one of which has the formula:



In our endeavor to provide a low cost, high yield process for preparing quinolone antibiotics, we desired to affect ring closure of 2-enamino- β -ketoester quinolone antibiotic precursor intermediates having the general formula:

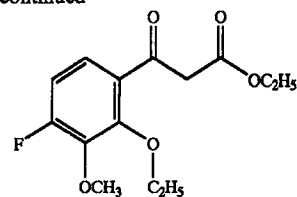


wherein X is a leaving group and R⁴ is a moiety which is compatible with the ring closure reaction conditions. To achieve these quinolone antibiotic intermediates we began our process by reacting 3-substituted-2,4-difluorobenzophenones with diethylcarbonate in the expectation of forming the corresponding β -ketoester. However, analysis of the products which result from the reaction of diethylcarbonate with 2,4-difluoro-3-methoxybenzophenone indicated an admixture of products as outlined below



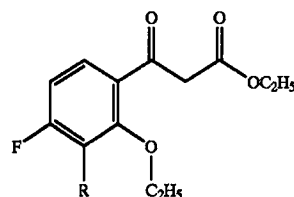
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-continued



wherein a substantial amount of the 2-position fluorine atom had been displaced by an ethoxy unit in an unwanted side reaction.

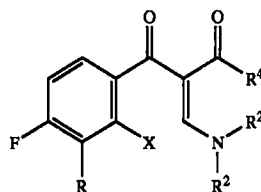
It has now been surprisingly discovered that the presence of an impurity having the general formula:



which is formed in substantial amounts as a by product of the reaction of 3-substituted 2,4-difluorobenzophenones with diethylcarbonate, can be successfully cyclized, together with the corresponding 2-fluoro adduct, in a ring closure reaction which affords the desired quinolone antibiotic intermediate in high yield and under mild conditions. It has also been surprisingly discovered that the R unit can be extended to include C₁-C₂ alkyl, C₁-C₂ fluoroalkyl, C₂-C₄ alkenyl, chloro, or bromo, as well as methoxy.

Process Intermediates

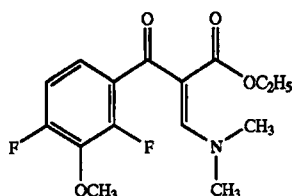
The process of the present invention described herein below, utilizes novel compounds as intermediates. These intermediates fall into two categories. The first category relates to β -ketoester enamines which are formed from the reaction of a secondary amine and a 3-aryl-3-oxo-propionic acid ester having the formula:



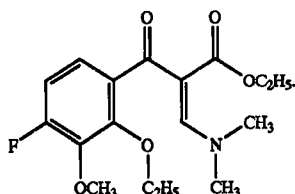
wherein R is C₁-C₂ alkyl, C₁-C₂ fluoroalkyl, C₂-C₄ alkenyl, methoxy, chloro, or bromo; R² is C₁-C₄ linear or branched alkyl, phenyl, and mixtures thereof; and R⁴ is a unit which is compatible with the subsequent ring closure reaction conditions. Non-limiting examples of a unit which is suitable as R⁴ is an alkoxy unit which results in the formation of a methyl ester. Ester are the most convenient moiety since the antibiotic which are formed from the intermediates described herein comprise a 3-carboxyquinolone.

A first aspect of the present invention as it relates to novel compounds encompasses R units equal to methoxy. An embodiment of this aspect of R has the formula:

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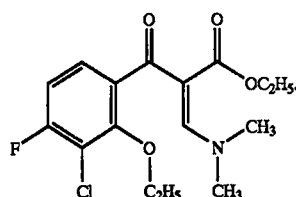


while another embodiment has the formula:



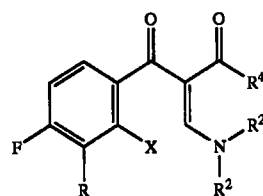
A second aspect relates to R units which are lower alkyl or fluorine substituted lower alkyl, iterations of which include $-\text{CH}_3$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, and $-\text{CF}_3$.

A third aspect relates to R units comprising chloro or bromo. An embodiment of this aspect of R has the formula:



A fourth aspect relates to R units comprising an olefin, inter alia, $-\text{CH}_2\text{CH}=\text{CH}_2$.

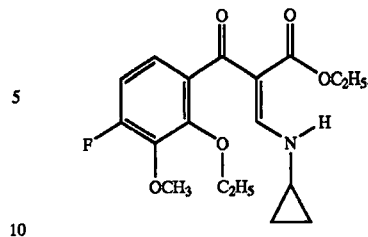
The second category relates to β -ketoester enamines which are formed from the reaction of a secondary amine and a 3-aryl-3-oxo-propionic acid ester having the formula:



wherein R is C_1 - C_2 alkyl, C_1 - C_2 fluoroalkyl, C_2 - C_4 alkenyl, methoxy, chloro, or bromo; R^2 is C_1 - C_4 linear or branched alkyl, phenyl, and mixtures thereof; and R^4 is a unit which is compatible with the subsequent ring closure reaction conditions.

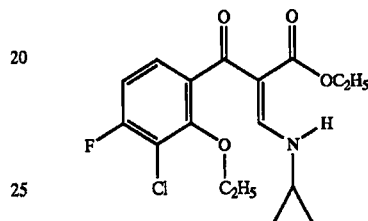
A first aspect relates to R equal to methoxy. An embodiment of this aspect of R has the formula:

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A second aspect relates to R units which are lower alkyl or fluorine substituted lower alkyl, iterations of which include $-\text{CH}_3$, $-\text{CH}_2\text{F}$, $-\text{CHF}_2$, and $-\text{CF}_3$.

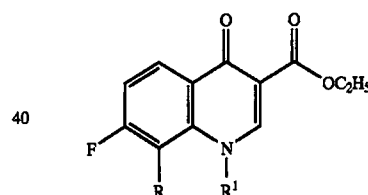
A third aspect relates to R units comprising chloro or bromo. An embodiment of this aspect of R has the formula:



A fourth aspect relates to R units comprising an olefin, inter alia, $-\text{CH}_2\text{CH}=\text{CH}_2$.

Process

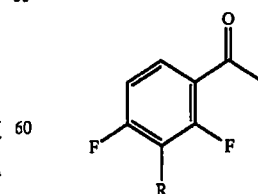
The process of the present invention relates to the preparation of quinolone antibiotic intermediates having the formula:



wherein R is C_1 - C_2 alkyl, C_1 - C_2 fluoroalkyl, C_2 - C_4 alkenyl, methoxy, chloro, or bromo; R^1 is a unit selected from the group consisting of C_1 - C_2 alkyl, C_2 - C_3 alkenyl, C_3 - C_5 cycloalkyl, and phenyl, each of which can be substituted by one or more fluorine atoms.

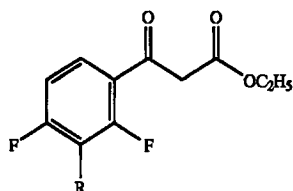
Step (a)

Step (a) of the present process relates to the reaction of a 3-substituted-2,4-difluorobenzophenone having the formula:

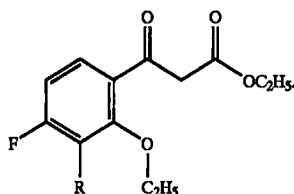


with diethylcarbonate in the presence of a base to form an admixture of 3-[2,4-difluoro-3-R-substituted]-3-oxo-propionic acid methyl ester:

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and 3-[2-ethoxy-3-R-substituted-4-fluoro]-3-oxo-propionic acid methyl ester:



The stoichiometry of Step (a) requires at least one equivalent of diethylcarbonate per equivalent of benzophenone. However, other aspects of Step (a) utilize amounts of diethylcarbonate in excess of one mole equivalent.

The stoichiometry of Step (a) also requires at least one equivalent of base. Suitable bases include metal hydrides, for example, LiH, NaH, KH, CaH₂, and the like. One aspect relating to the selection of a base utilizes mineral oil suspension of NaH which can be used conveniently and safely in large scale, as well as small scale operations. Other bases include inorganic bases, inter alia, Na₂CO₃, NaHCO₃, and K₂CO₃ or organic bases, inter alia, butyl lithium and lithium diisopropylamide.

One aspect of the present invention relates to the use of an excess of diethylcarbonate. A first iteration of Step (a) wherein an excess of diethylcarbonate is used encompasses the concomitant use of excess base as well. A non-limiting example of Step (a) related to this aspect includes the reaction of one mole of a 2,4-difluoro-3-R-substituted benzophenone, 2.2 moles of a base, and 2.4 moles of diethylcarbonate.

The formulator may use an aprotic solvent for step (a) both to solubilize the reagents and to provide an efficient heat transfer medium. Non-limiting examples of solvents include methylene chloride, dichloromethane, hexamethylphosphoramide, tetrahydrofuran, benzene, toluene, alkanes, inter alia, hexane, or mixtures of solvents. Most conditions require the use of moisture free solvents, however, the formulator may employ excess base to consume any residual or nascent water which is present. One aspect of the present invention relates to the use of toluene as a solvent, which in the case of processes which do not isolate intermediates, can be used to azeotropically dry the reaction product.

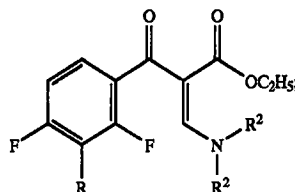
The temperature at which Step (a) is conducted is predicated on several factors, including the reactivity of the starting benzophenone, the choice of base, and the freezing/boiling point of any solvent which is used. One example of the present invention, as it relates to the temperature of step (a), is described herein below in Example 1 wherein the diethylcarbonate is slowly added to a suspension of the base (NaH) in toluene at 90° C. followed by addition of the acetophenone at 90° C.-95° C. However, depending upon the choice of reagents and the scale of the reaction, the formulator may choose to complete the reaction at lower temperatures.

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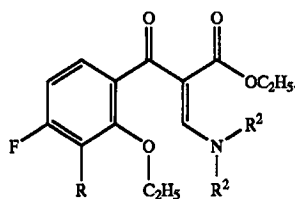
One aspect relates to initial de-protonation of the benzophenone with an alkyl lithium reagent in the cold and allowing the solution to warm prior to addition of the diethylcarbonate.

Step (b)

Step (b) of the present invention relates to the reaction of the admixture formed in Step (a) with an adduct which is capable of undergoing a Knoevenagel or Knoevenagel-like reaction to form an admixture of N,N-disubstituted enamines having the formula:



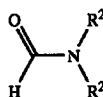
and the formula:



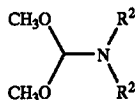
The adduct which is reacted with the β -ketoester admixture formed in Step (a) has the formula:



wherein R² is C₁-C₄ linear or branched alkyl, phenyl, and mixtures thereof; X is an aldehyde unit or an aldehyde unit equivalent. What is meant herein by the definition of X is that the adduct may be an aldehyde having the formula:



or an aldehyde equivalent, for example, a dimethyl acetal having the formula:



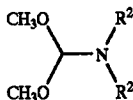
Depending upon the conditions of Step (b) the formulator may select any form for the adduct provided it is capable of forming the required admixture of enamines.

The stoichiometry of Step (b) requires at least one equivalent of the aldehyde or aldehyde-equivalent adduct per equivalent of benzophenone in all forms. However, other aspects of Step (b) utilize amounts of the adduct in excess of one mole equivalent.

One aspect of the present invention relates to the use of an excess of an adduct which comprises an aldehyde equivalent.

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lent. A non-limiting example of Step (b) related to this aspect includes the reaction of one mole of the β -ketoester admixture with 1.5 mole equivalents of a dimethyl acetal having the formula:



for example, the reaction as outlined herein below in Example 1.

Typically the β -ketoester admixture and the adduct are combined together at room temperature and heated. In the case of acetal comprising aldehyde equivalents, the reaction can be driven to completion by distilling off the alcohol which is released then the aldehyde carbonyl reacts with the β -ketoester admixture.

The formulator may use any solvent for Step (b), which does not react with the reagents under the conditions of the step, both to solublize the reagents and to provide an efficient heat transfer medium. Non-limiting examples of solvents include methylene chloride, dichloromethane, hexamethylphosphoramide, tetrahydrofuran, benzene, toluene, alkanes, inter alia, hexane, or mixtures of solvents. However, alcoholic solvents, especially in the presence of aldehyde equivalents may severely limit the reactivity of the adduct and therefore should not be used. One aspect of the present invention relates to the use of toluene as a solvent, which in the case of processes which do not isolate intermediates, can be used to azeotropically dry the reaction product.

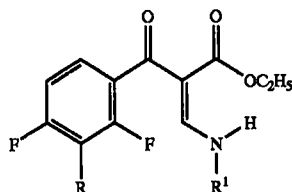
The temperature at which Step (b) is conducted is predicated on several factors, including the reactivity of the aldehyde-comprising or aldehyde equivalent-comprising adduct and the freezing/boiling point of any solvent which is used. Example 1 herein below provides a suitable example for the temperature range at which each facet of Step (b) is conducted.

Step (c)

Step (c) of the present process relates to the reaction of the N,N-disubstituted enamine admixture formed in Step (b) with a primary amine having the formula:

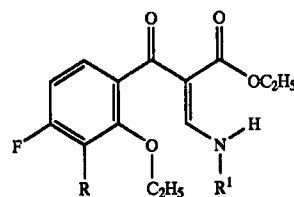


to form an admixture of quinolone intermediates having the formula:



and the formula:

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wherein R^1 is a unit selected from the group consisting of C_1 - C_2 alkyl, C_2 - C_3 alkenyl, C_3 - C_5 cycloalkyl, and phenyl, each of which can be substituted by one or more fluorine atoms.

The stoichiometry of Step (c) requires at least one equivalent of the amine per total amount of enamine present in the admixture. However, other aspects of Step (c) utilize amounts of the amine in excess of one mole equivalent.

The formulator may use an aprotic solvent for step (c) both to solublize the reagents and to provide an efficient heat transfer medium. Non-limiting examples of solvents include methylene chloride, dichloromethane, hexamethylphosphoramide, tetrahydrofuran, benzene, toluene, alkanes, inter alia, hexane, or mixtures of solvents. Most conditions require the use of moisture free solvents, however, the formulator may employ excess base to consume any residual or nascent water which is present. One aspect of the present invention relates to the use of toluene as a solvent, which in the case of processes which do not isolate intermediates, can be used to azeotropically dry the reaction product.

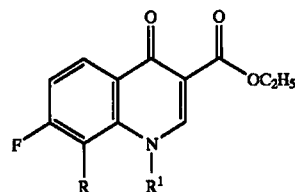
Typically the amine can be added as a solution in a suitable solvent, or directly to the reaction admixture if the amine is a liquid. Step (c) may be conducted at any temperature which is sufficient to complete the reaction. One embodiment, which is exemplified in Example 1 herein below, conducts the reaction at room temperature.

One aspect of the present invention relates to the use of an excess of the amine. A first iteration of Step (c) wherein an excess of an amine is used encompasses a work-up for neutral product which comprises treatment of the reaction solution with acid.

The flexibility of the present process is manifest in the fact the formulator can optionally combine Steps (b) and (c) in manner wherein the admixture formed in Step (b) is not isolated, but instead is carried forward to Step (c). This option allows the formulator the advantage of large batch production of the quinolone antibiotic intermediates once the reaction parameters have been determined.

Step (d)

Step (d) of the present process relate to cyclizing the quinoline intermediate admixture formed in Step (c) in the presence of a silylating agent to form a quinoline antibiotic intermediate having the formula:



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What is meant herein by "silylating agent" is any "organosilicon" compound or any silicon-containing compound that is commonly utilized in silylation reactions, wherein a hydrogen atom, inter alia, nitrogen, oxygen, is substituted with a silyl group. Non-limiting examples of silyl groups include trimethylsilyl and phenyldimethylsilyl. Non-limiting examples of silylating agents include: chlorotrimethylsilane, N,O-bis(trimethyl-silyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, bis(trimethylsilyl)urea, hexamethyltrisilazane, N-methyl-N-trimethylsilyltrifluoroacetamide, 1-trimethylsilyl-imidazole, trimethylsilyl trifluoromethanesulfonate, tert-butyltrimethylchlorosilane, 1-(tert-butyltrimethylsilyl)imidazole, N-tert-butyltrimethyl-N-methyltrifluoroacetamide, tert-butyltrimethylsilyltrifluoromethanesulfonate, tert-butylphenylchlorosilane, tert-butylmethoxyphenylbromosilane, dimethylphenylchlorosilane, triethylchlorosilane, trimethyl-silyl trifluoromethanesulfonate, and triphenylchlorosilane. The use of silylating agent is described by Cooper, B., "Silylation in Organic Synthesis", *Proc. Biochem.* 9, (1980) included herein by reference. The use of silylating agents for quinolone formation is further described in U.S. Pat. No. 5,801,242 Randall et al., issued Sep. 1, 1998; and U.S. Pat. No. 5,703,231 Randall et al., issued Dec. 30, 1997 both of which are incorporated herein by reference.

Not wishing to be limited by theory, the proposed stoichiometry of Step (d) requires at least one equivalent of silylating agent for each equivalent of enamine in the admixture formed in Step (c). However, other aspects of Step (d) utilize amounts of the silylating agent in excess of one mole equivalent.

The formulator may use an aprotic solvent for step (c) both to solublize the reagents and to provide an efficient heat transfer medium. Non-limiting examples of solvents include methylene chloride, dichloromethane, hexamethylphosphoramide, tetrahydrofuran, benzene, toluene, alkanes, inter alia, hexane, or mixtures of solvents, inter alia, hexane, or mixtures of solvents. Most conditions require the use of moisture free solvents, however, the formulator may employ excess base to consume any residual or nascent water which is present. One aspect of the present invention relates to the use of toluene as a solvent, which in the case of processes which do not isolate intermediates, can be used to azeotropically dry the reaction product.

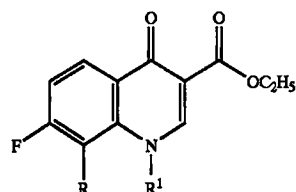
Typically the silylating agents are liquids which can be added directly to the reaction solution of the enamine admixture formed in Step (c) or the silylating agents are low melting solids that can be added as a solution in a suitable solvent. Step (d) may be conducted at any temperature which is sufficient to complete the reaction. One embodiment, which is exemplified in Example 1 herein below, adds the silylating agent at room temperature then heats the reaction to reflux in a suitable solvent until the reaction is complete.

The flexibility of the present process allows for a continuous batch process wherein the intermediate admixtures do not have to be isolated from the product matrix and purified. It is also convenient that the steps of the present process can be conveniently monitored for completion by

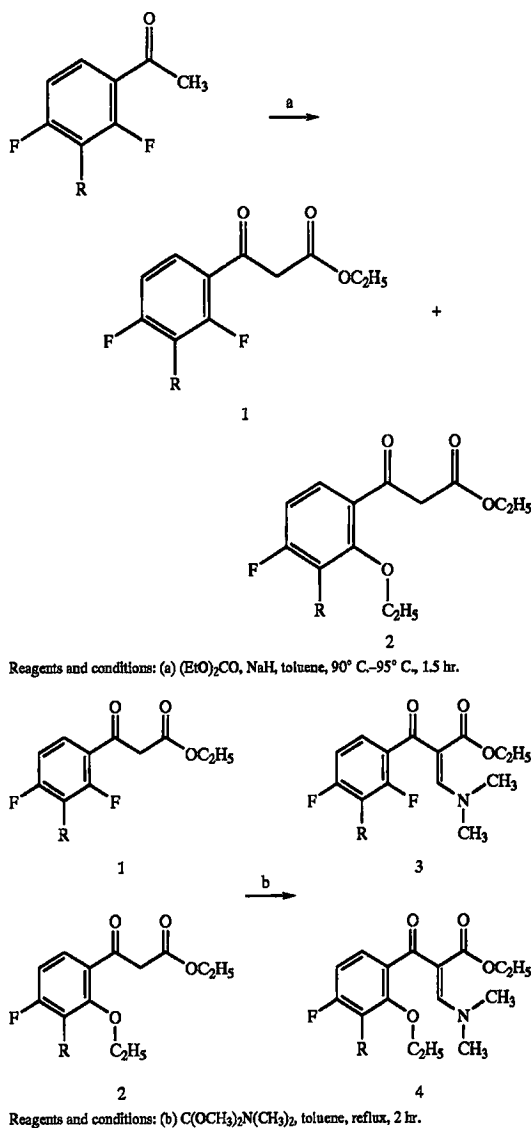
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thin layer chromatography (TLC) or any conventional analytical HPLC system.

The first category of quinolone antibiotic intermediates which are capable of being prepared by the process of the present invention are 3-carboxyquinolone methyl esters having the formula:

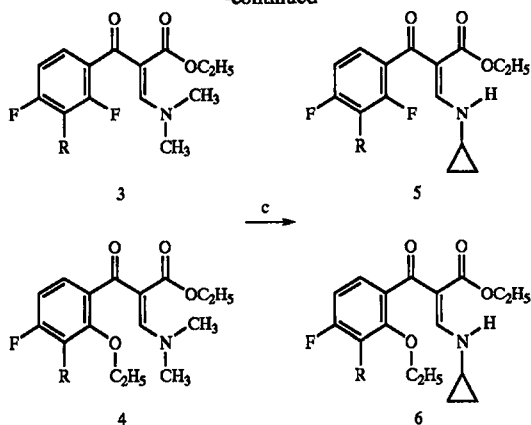


The following scheme and Example 1 illustrate the present process for preparing compounds of category one, wherein for the present example R is methoxy and R¹ is cyclopropyl.

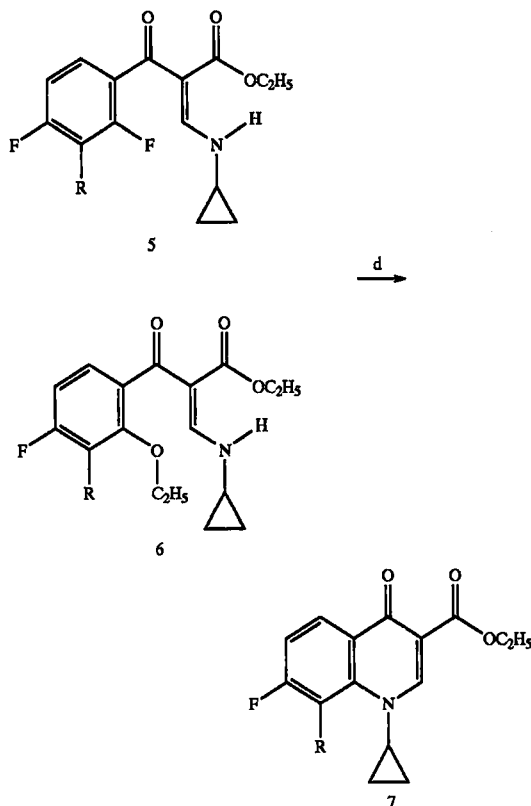


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-continued



Reagents and conditions: (c) cyclopropylamine, toluene, rt, 1 hr.



Reagents and conditions: (d) N,O-bis(trimethylsilyl)acetamide, toluene, reflux, 1 hr.

EXAMPLE 1

7-Fluoro-8-methoxyquinolone Ethyl Ester (7)

Preparation of 3-(2,4-difluoro-3-methoxyphenyl)-3-oxo-propionic acid ethyl ester and 3-(2-ethoxy-4-difluoro-3-methoxyphenyl)-3-oxo-propionic acid ethyl ester admixture (1 and 2): To a reaction vessel is charged toluene (2087 mL) and an oil dispersion of NaH containing 60% active base (264 g, 6.6 mol). Diethylcarbonate (850.5 g, 7.2 mol) is slowly added over 1 hour to the suspension of NaH at 90° C. 2,4-Difluoro-3-methoxyacetophenone (558 g, 3 mol) is dissolved in sufficient toluene to form a homogeneous solution (approx. 2 L) and this solution is added with care to the reaction vessel maintaining the reaction temperature

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within the range of 90° C.-95° C. Once the evolution of hydrogen gas has stopped, the reaction is stirred an additional 30 minutes after which the reaction is cooled to 20° C. and quenched with the addition of a 10% w/w aqueous solution of H₂SO₄ (3822 g). The layers are separated and the solvent is concentrated in vacuo (40° C. @ <100 mbar), the toluene azeotrope utilized to dry the organic phase. The resulting admixture of compounds 1 and 2 is used without further purification.

Preparation of 2-(2,4-difluoro-3-methoxybenzoyl)-3-dimethylamino-acrylic acid ethyl ester and 2-(2-ethoxy-3-methoxy-4-fluorobenzoyl)-3-dimethylamino-acrylic acid ethyl ester admixture (3 and 4): To a reaction vessel is charged an admixture of 3-(2,4-difluoro-3-methoxyphenyl)-3-oxo-propionic acid ethyl ester and 3-(2-ethoxy-4-fluoro-3-methoxyphenyl)-3-oxo-propionic acid ethyl ester, 1 & 2, (850 g, ~3 mol) and toluene (3850 mL). Over a period of about 15 minutes dimethylformamide dimethyl acetal (536.3 g, 4.5 mol) is added after which the reaction is heated to about 90° C. and the methanol produced is allowed to distill off. The solution is then refluxed for about 2 hours. At this point the reaction sequence can be carried forward without isolation of 3 and 4. The products are isolated by concentrating the reaction solution in vacuo, taking up the residue in methylene chloride and extracting the resulting organic layer with water. Re-concentration in vacuo provides the admixture of 3 and 4.

Preparation of 3-cyclopropylamino-2-(2,4-difluoro-3-methoxybenzoyl)-acrylic acid ethyl ester and 3-cyclopropylamino-2-(2-ethoxy-3-methoxy-4-fluorobenzoyl)-acrylic acid ethyl ester admixture (5 and 6): The reaction from above, the admixture of 3 and 4, at the point after which the solution has been refluxed for about 2 hours, is cooled to room temperature and toluene is added (2087 mL). Cyclopropylamine (205.6 g, 3.6 mol) is added and stirring is continued at room temperature until the reaction is complete by TLC (about 30 minutes). The reaction is then quenched by adding a 10% aqueous solution of H₂SO₄ (2940 g, 3 mol). The organic layer is concentrated in vacuo until all presence of water is absent. The resulting toluene solution of 5 and 6 can be carried on to the ring closure reaction without further purification.

Preparation of 1-cyclopropyl-7-fluoro-8-methoxy-4-oxo-1,4-dihydro-quinoline-3-carboxylic acid ethyl ester admixture of 3-cyclopropylamino-2-(2,4-difluoro-3-methoxybenzoyl)-acrylic acid ethyl ester and 3-cyclopropylamino-2-(2-ethoxy-3-methoxy-4-fluorobenzoyl)-acrylic acid ethyl ester, 5 and 6, (1050 g, ~3 mol) and toluene (4270 mL). N,O-Bis(trimethylsilyl)-acetamide (610.3 g, 3 mol) is added and the reaction is brought to reflux for 30 minutes. Additional N,O-bis(trimethylsilyl)-acetamide (183 g, 0.9 mol) is added to the reaction and heating is continued for an additional 30 minutes. The reaction is cooled and the solvent reduced in vacuo (40° C. @, 100 mbar). The solution is cooled in an ice bath and the solid which forms is collected by filtration, and wash twice with distilled water to afford 757 g (82% yield) of the desired product.

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.

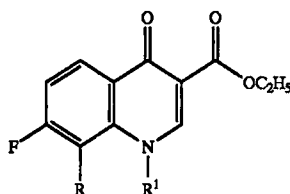
While particular embodiments of the present invention have been illustrated and described, it would be obvious to those skilled in the art that various other changes and

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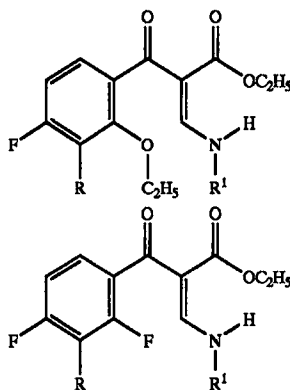
modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this invention.

What is claimed is:

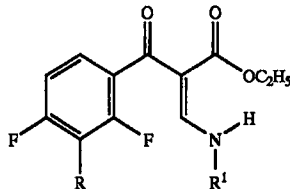
1. A process for preparing a quinolone antibiotic intermediate having the formula:



wherein R is C₁-C₂ alkyl, C₁-C₂ fluoroalkyl, C₂-C₄ alkenyl, methoxy, chloro, or bromo; R¹ is a unit selected from the group consisting of C₁-C₂ alkyl, C₂-C₃ alkenyl, C₃-C₅ cycloalkyl, and phenyl, each of which can be substituted by one or more fluorine atoms; said process comprising the step of cyclizing an admixture of quinolone precursors, said admixture comprising a 2-ethoxy substituted intermediate having the formula:



and



in the presence of a silylating agent.

2. A process according to claim 1 wherein R is -OCH₃.
3. A process according to claim 1 wherein R is -CH₃, -CH₂F, -CHF₂, and -CF₃.
4. A process according to claim 1 wherein R is -Cl.
5. A process according to claim 1 wherein R is -CH₂CH=CH₂.

6. A process according to claim 1 wherein said cyclization is conducted in the presence of a solvent selected from the group consisting of methylene chloride, dichloromethane, hexamethylphosphoramide, tetrahydrofuran, benzene, toluene, alkanes, and mixtures thereof.

7. A process according to claim 1 wherein said silylating agent is selected from the group consisting of chlorotrimethylsilane, N,O-bis(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, bis(trimethylsilyl)urea, hexamethyltrisilazane, N-methyl-N-trimethylsilyltrifluoroacetamide, 1-trimethylsilyl-imidazole, trimethylsilyl trifluoromethanesulfonate, tert-butyltrimethylchlorosilane, 1-(tert-butyltrimethylsilyl)imidazole, N-tert-butyltrimethyl-N-methyltrifluoroacetamide, tert-butyltrimethylsilyltrifluoromethanesulfonate, tert-butylphenylchlorosilane, tert-butylmethoxyphenylbromosilane, dimethylphenylchlorosilane, triethylchlorosilane, trimethylsilyl

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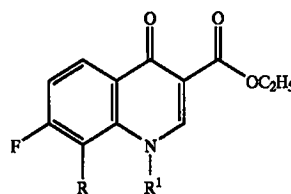
methoxyphenylbromosilane, dimethylphenylchlorosilane, triethylchlorosilane, trimethylsilyltrifluoromethanesulfonate, and triphenylchlorosilane.

8. A process according to claim 7 wherein said silylating agent is N,O-bis(trimethylsilyl)acetamide.

9. A process according to claim 1 wherein R¹ cyclopropyl, methyl, ethyl, and benzyl.

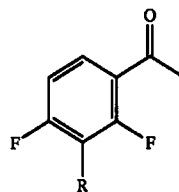
10. A process according to claim 1 wherein said cyclization is conducted by refluxing in the presence of a solvent.

11. A process for preparing a quinolone antibiotic intermediate having the formula:

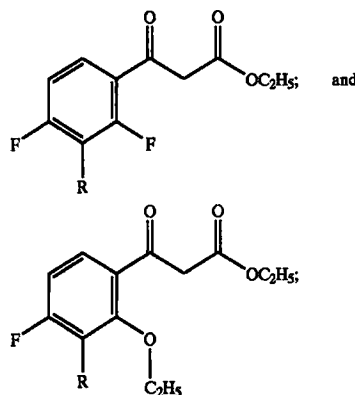


wherein R is C₁-C₂ alkyl, C₁-C₂ fluoroalkyl, C₂-C₄ alkenyl, methoxy, chloro, or bromo; R¹ is a unit selected from the group consisting of C₁-C₂ alkyl, C₂-C₃ alkenyl, C₃-C₅ cycloalkyl, and phenyl, each of which can be substituted by one or more fluorine atoms; said process comprising the steps of:

a) reacting an acetophenone having the formula:

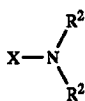


with diethylcarbonate in the presence of a base to form an admixture of 4-fluoro β-ketoesters having the formula:

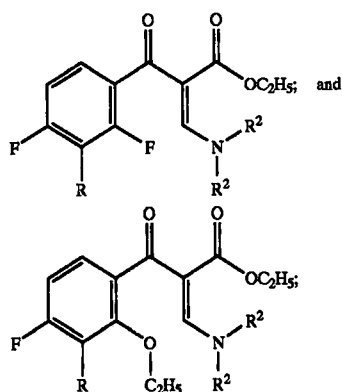


b) reacting said admixture with a compound capable of undergoing the Knoevenagel Reaction having the formula:

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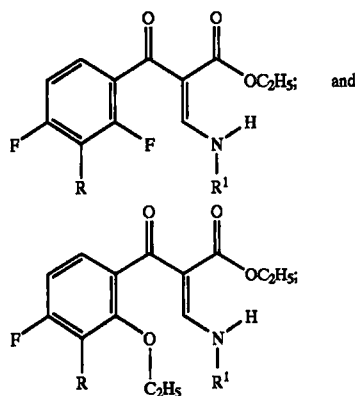
wherein R^2 is C_1 - C_4 linear or branched alkyl, phenyl, and mixtures thereof; X is an aldehyde unit or an aldehyde unit equivalent; to form an admixture of imine intermediates having the formula:



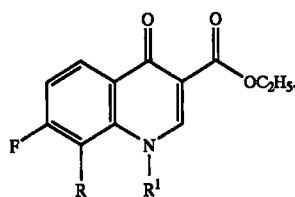
c) reacting said imine intermediate admixture with an amine having the formula:



to form an admixture of quinolone intermediates having the formula:



d) cyclizing said quinoline intermediate admixture in the presence of a silylating agents to form said quinolone antibiotic intermediate having the formula:



12. A process according to claim 11 wherein said base in step (a) is a metal hydride selected from the group LiH, NaH, KH, CaH_2 and mixtures thereof.

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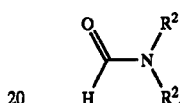
13. A process according to claim 11 wherein said base in step (a) is an inorganic base selected from the group Na_2CO_3 , NaHCO_3 , K_2CO_3 and mixtures thereof.

14. A process according to claim 11 wherein said base in step (a) an organic base selected from butyl lithium and lithium diisopropylamide.

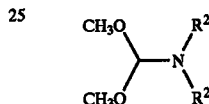
15. A process according to claim 11 wherein step (a) comprises reacting one mole of a substituted acetophenone with 2.2 moles of a base, and 2.4 moles of diethylcarbonate.

16. A process according to claim 11 wherein step (a) is conducted in the presence of a solvent selected from the group consisting of methylene chloride, dichloro-methane, hexamethylphosphoramide, tetrahydrofuran, benzene, toluene, alkanes, and mixtures thereof.

17. A process according to claim 11 wherein said adduct is an aldehyde having the formula:



18. A process according to claim 11 wherein said adduct is a dimethyl acetal having the formula:



wherein R^2 is methyl, ethyl, and mixtures thereof.

19. A process according to claim 11 wherein step (b) is conducted in the presence of toluene wherein said adduct is a dimethyl acetal and wherein further the admixture obtained from step (a) and said dimethyl acetal is heated to azeotropically remove any methanol which is formed.

20. A process according to claim 11 wherein said primary amine in step (c) is selected from the group consisting of methylamine, ethylamine, and cyclopropylamine.

21. A process according to claim 11 wherein step (a) is conducted in the presence of a solvent selected from the group consisting of methylene chloride, dichloro-methane, hexamethylphosphoramide, tetrahydrofuran, benzene, toluene, alkanes, and mixtures thereof.

22. A process according to claim 11 wherein step (d) is conducted in the presence of a solvent selected from the group consisting of methylene chloride, dichloromethane, hexamethylphosphoramide, tetrahydrofuran, benzene, toluene, alkanes, and mixtures thereof.

23. A process according to claim 11 wherein said silylating agent is selected from the group consisting of chlorotrimethylsilane, N,O-bis(trimethyl-silyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, bis(trimethylsilyl)urea, hexamethyltrisilazane, N-methyl-N-trimethylsilyltrifluoroacetamide, 1-trimethylsilyl-imidazole, trimethylsilyl trifluoromethanesulfonate, tert-butyltrimethylchlorosilane, 1-(tert-butyltrimethylsilyl)imidazole, N-tert-butyltrimethyl-N-methyltrifluoroacetamide, tert-butyltrimethylsilyltrifluoromethane sulfonate, tert-butylphenylchlorosilane, tert-butyl-methoxyphenylbromosilane, dimethylphenylchlorosilane, triethylchlorosilane, trimethylsilyl trifluoromethanesulfonate, and triphenylchlorosilane.

24. A process according to claim 23 wherein said silylating agents is N,O-bis(trimethylsilyl)acetamide.

25. A process according to claim 11 wherein atop (d) is conducted by reflecting in the presence of a solvent.

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