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FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL

1

SOLICITUD DE:

☒ Patente de invención.

☐ Patente de Modelo de Utilidad.

☐ Capítulo I.

☒ Capítulo II.

2

SOLICITANTE
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Lugar de Constitución: Suecia

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C.E. ☐ Otro ☐

Cual _____

Número _____

3

REPRESENTANTE
O APODERADO

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Número 170.322 TP 1003

4

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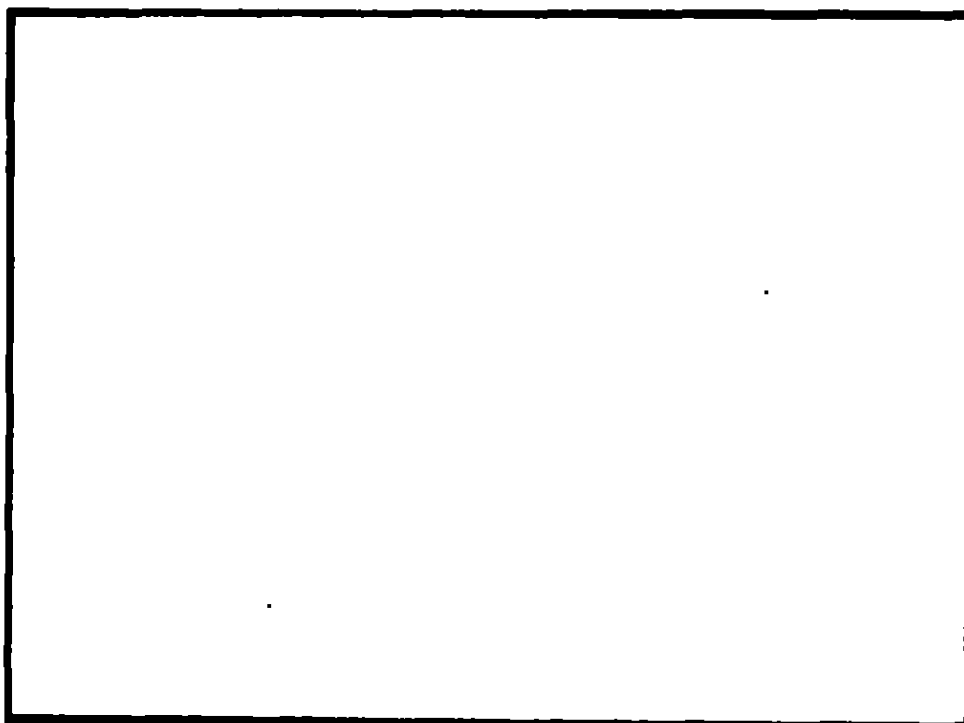
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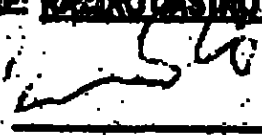
ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$378.000
- ☒ Comprobante de pago por reivindicación de prioridad. \$212.000
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. Fotocopia Autenticada Anesa
- ☐ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☐ Arte final 12x12.
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☐ Otros

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente.

NOMBRE: RAMIRO CASTRO DUQUEFIRMA: 

C.C. 170.322 de Bogotá T.P. 1003 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

Industria y Comercio
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Radicación : 02109616 00000000 Folios: 66
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Superintendencia 2520 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 02 73,259
FECHA : OCTUBRE 31 DE 2002

******* CORRELACION *******

DEPOSITANTE	TIPO PAIS	ORIGEN	CLASIFICACION	LS. PAIS	FECHA REC	V. PAIS
OT S CASTRO LTDA	COLOMBIA	DEPTO BOYACA	056-00110-6	1326347	31/10/2002	7,126,630.30

******* CONCEPTO *******

CANT. REGISTRADO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 COLECCIONES	1 TRAMITES DE SOL. DE PATENTE DE IN	376,630.30
	TOTAL :	376,630.30

COTIZACION TRESCIENTOS SETENTA Y SEIS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE N°

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Dependencia: 2000 DIVISION DE NUEVOS CREACIONES

RECIBO OFICIAL DE CAJA : 02 - 74,236
FECHA : DICIEMBRE 6 DE 2002

***** CONSIGNACION *****

CONSIGNANTE	TIPO PAGO	EMISOR	CUENTA	NO. PAGO	FECHA PAGO	VR. PAGO
PRECARIO & CASTRO LTDA	CONSIGNACION	EMISOR TITULAR	020-00110-5	5165222	05/11/2002	7,470,960.00

***** C E N T R O P Y C *****

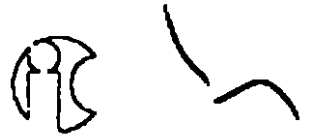
CANT. RESERVACION	CONCEPTO	TOTAL CONCEPTO
1	00015 01 DELICITUDES	104,000.00
	115 PTO CAP-11: EMISOR DE PATENTACION	101,870.00
	TOTAL :	205,870.00

COS: CIENTO SEIS MIL PESOS

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Bogotá, D.C., Colombia



Industria y Comercio
SUPERINTENDENCIA

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Dedicacion: 02309618 00000000
Fecha (BBO): 2002-12-03 16:19:23
Tramite: 011 PCT-PATENT 129 FASE INCI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO DE PAGOS DE CAJA : 02 - 74,237
FECHA : NOVIEMBRE 5 DE 2002

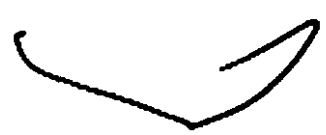
***** CONSULTA *****

DEPOSITANTE	TIPO PAGO	PAIS	NUMERO	Co. PAGO	FECHA PAGO	T. PAGO
BOYACAS & CASTRO LTDA	DEPOSITO	COLOMBIA	650-3010-6	5155332	06/11/2002	7,470,000.00

***** C O N T A B L E *****

CANT. RELACIONES	CONCEPTO	TOTAL CONCEPTO
1 SOLICITUDES	110 FIC 2002 EXAMEN DE PATENTABILIDAD	106,630.30
	TOTAL	106,630.30

DE: CEBAS SEIS MIL PESOS



RESPONSABLE: _____

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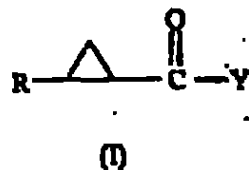
PROCESO PARA LA PREPARACIÓN DE ÉSTERES DE ÁCIDO CARBOXÍLICO CICLOPROPIL Y DERIVADOS

CAMPO DE LA INVENCION

La presente invención se relaciona con un novedoso proceso para la preparación de algunos ésteres de ácido carboxílico y otros derivados de ácido carboxílico ciclopropil; un novedoso proceso para la preparación de dimetilsulfoxonio metilida y dimetilsulfonio metilida; al uso de algunos ésteres de ácido carboxílico ciclopropil en un proceso para la preparación de intermediarios que pueden usarse en la síntesis de entidades farmacéuticamente activas; y a algunos intermediarios proporcionados por estos procesos.

DESCRIPCIÓN DE LA INVENCION

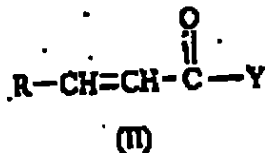
En un primer aspecto la invención proporciona consecuentemente un proceso para la preparación de un compuesto de fórmula (I):



donde:

R es fenil sustituido con uno o más halógenos;

Y es OR¹, donde R¹ es un alquil de cadena recta, alquil ramificado, cicloalquil, o un grupo bicicloheptil sustituido (por ejemplo bornil), el cual comprende contactar un compuesto de fórmula (II):



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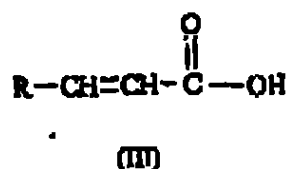
donde R e Y son como se definió arriba, con dimetilsulfoxonio metilida en presencia de un solvente.

Adecuadamente el solvente es un solvente polar, preferiblemente dimetilsulfóxido. Adecuadamente, la reacción se lleva a cabo a -10°C hasta -90°C , preferiblemente a 25°C .

El dimetilsulfoxonio metilida puede prepararse reaccionando una sal trimetilsulfoxonio con una base sólida fuerte, preferiblemente en forma sólida, en dimetil sulfóxido a temperatura ambiente o temperatura elevada. Adecuadamente, la base es un hidróxido de metal, por ejemplo NaOH , LiOH , o hidrido de metal alcalino, por ejemplo NaH . Preferiblemente la base es hidróxido de sodio.

Preferiblemente, el ioduro trimetilsulfoxonio se agita con polvo de hidróxido de sodio en dimetil sulfóxido (en ausencia de un catalizador de transferencia de fase), opcionalmente bajo nitrógeno a 20 hasta 25°C durante 90 minutos. Alternativamente, el dimetilsulfoxonio metilida puede prepararse a partir de una sal trimetilsulfoxonio (preferiblemente ioduro o cloruro) usando hidróxido de sodio en dimetil sulfóxido con un catalizador de transferencia de fase, por ejemplo tetrabutyl-n-bromuro de amonio, o con otras bases fuertes, tales como hidridos de metal alcalino, en dimetil sulfóxido.

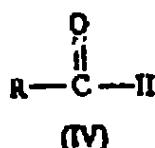
Un compuesto de fórmula (II) puede prepararse reaccionando un compuesto de fórmula (III):



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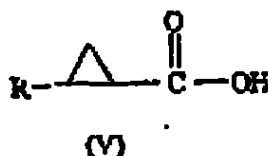
donde R es como se definió arriba, con un adecuado agente de clorinación en presencia de un solvente inerte y un catalizador opcional a una temperatura de 0 a 200°C. Preferiblemente Y OR¹, el agente de clorinación es cloruro de tionil, el solvente inerte es tolueno, y el catalizador es piridina. Adecuadamente la temperatura de la reacción es 70°C. El cloruro ácido resultante se reacciona entonces con YH o Y⁻ (donde Y⁻ es una especie aniónica de Y), Y es como se definió arriba, opcionalmente a una elevada temperatura, tal como 100°C.

Un compuesto de fórmula (III) puede prepararse usando química estándar, por ejemplo contactando un compuesto de fórmula (IV):



donde R es como se definió arriba, con ácido malónico en presencia de piridina y piperidina a una elevada temperatura, preferiblemente 50 a 90°C.

Un compuesto de fórmula (I) puede hidrolizarse usando hidrólisis básica para lograr un compuesto de fórmula (V):

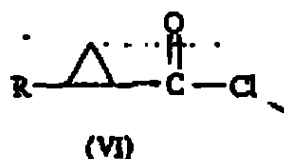


donde R es como se definió arriba. Por ejemplo, grupos éster se retiran preferiblemente mediante hidrólisis básica usando un hidróxido de metal alcalino, tal como hidróxido de sodio o hidróxido de litio, o hidróxido de amonio cuaternario en un solvente, tal como agua, un alcohol acuoso o

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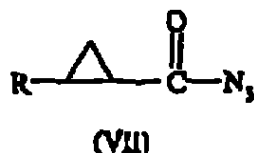
tetrahidrofuran acuoso, a una temperatura de desde 10 a 100°C. Más preferiblemente la base es hidróxido de sodio, el solvente es etanol, y la temperatura de la reacción es 50°C.

Un compuesto de fórmula (V) puede usarse para generar un compuesto de fórmula (VI):



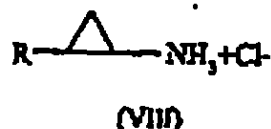
donde R es como se definió arriba, mediante la reacción con cloruro de tionil u otro agente de clorinación adecuado en presencia de tolueno, u otro solvente adecuado, y un catalizador opcional, preferiblemente piridina, a 0 a 200°C. Preferiblemente la temperatura está a 65 a 70°C.

Un compuesto de fórmula (VI) se puede usar en la síntesis de un compuesto de fórmula (VII):



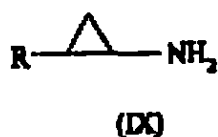
donde R es como se definió arriba, mediante la reacción con un ázido de metal alcalino (preferiblemente ázido de sodio) en presencia de un catalizador de transferencia de fase (preferiblemente tetra-n-butilamonio bromuro), carbonato de potasio acuoso y un solvente inerte (preferiblemente tolueno). Preferiblemente la temperatura de la reacción es de 0 a 10°C.

Un compuesto de fórmula (VII) puede usarse en la síntesis de un compuesto de fórmula (VIII):



donde R es como se definió arriba, por re-arreglo en tolueno a temperaturas entre 0°C y 200°C, preferiblemente a una temperatura de reacción de 90 a 100°C, después de lo cual el intermediario isocianato se reacciona con ácido clorhídrico a elevadas temperaturas, preferiblemente 85 a 90°C.

Una amina pariente no protonada (base libre) de fórmula (IX):



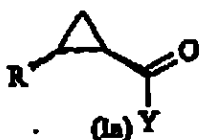
donde R es como se definió arriba, puede liberarse ajustando el pH de una solución acuosa de la sal de un compuesto de fórmula (VIII) a 10 o más. Esto puede entonces convertirse a otras sales de ácidos orgánicos o ácidos inorgánicos, preferiblemente ácido mandélico. La sal de R-(-)-ácido mandélico de un compuesto de fórmula (IX) puede generarse mediante la adición del R-(-)-ácido mandélico a temperatura ambiente o temperatura elevada a una solución de un compuesto de fórmula (IX) en un solvente, preferiblemente acetato de etilo. Preferiblemente la temperatura es de 20°C.

Adecuadamente R es fenil opcionalmente sustituido por uno o más átomos halógenos. Preferiblemente, R es fenil sustituido por uno o más átomos de flúor. Más preferiblemente R es 4-fluorofenil o 3,4-difluorofenil.

Preferiblemente Y es D-mentoxi, o más preferiblemente, L-mentoxi.

Los compuestos de las fórmulas (I) a (IX) pueden existir en diferentes formas isoméricas (tal como cis/trans, enantiómeros, o diastereoisómeros). El proceso de esta invención incluye todas estas formas isoméricas y sus mezclas en todas las proporciones.

Donde Y es chiral, un compuesto de fórmula (I) puede ser una mezcla de diastereoisómeros y puede resolverse para lograr un compuesto enriquecido diastereoméricamente de fórmula (Ia):

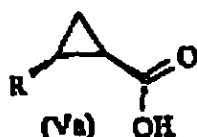


donde R e Y son como se definió arriba, por cristalización o por métodos cromatográficos.

Preferiblemente la cristalización se lleva a cabo in situ después de la síntesis de un compuesto de fórmula (I), como se describió arriba, calentando la mezcla cruda de la reacción mixture hasta que se logra la total o casi total disolución, luego se enfría a una velocidad apropiada hasta que se forman suficientes cristales de la calidad deseada. Los cristales se recogen entonces mediante filtración. Alternativamente, la resolución puede llevarse a cabo en cualquier otro solvente adecuado, tal como un hidrocarburo, por ejemplo heptano extrayendo un compuesto de

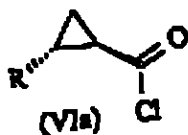
fórmula (1) en una cantidad adecuada del solvente, calentando los extractos hasta que se logra la total disolución, luego se enfría a una velocidad apropiada hasta que se forman suficientes cristales de la calidad deseada. Opcionalmente los extractos orgánicos pueden lavarse con agua, secarse sobre sulfato de magnesio y filtrarse antes de la cristalización descrita arriba.

Un compuesto de fórmula (1a) puede hidrolizarse para lograr el compuesto de fórmula (Va):



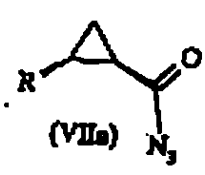
donde R es como se definió arriba, usando el método descrito arriba para la hidrólisis de un compuesto de fórmula (I) para lograr un compuesto de fórmula (V).

Un compuesto de fórmula (Va) puede usarse para generar un compuesto de fórmula (VIa):



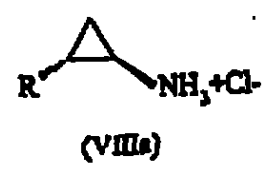
donde R es como se definió arriba, usando el método descrito arriba para la conversión de un compuesto de fórmula (V) para lograr un compuesto de fórmula (VI).

Un compuesto de fórmula (VIa) puede usarse en la síntesis de un compuesto de fórmula (VIIa):



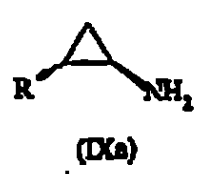
donde R es como se definió arriba, usando el método descrito arriba para la conversión de un compuesto de fórmula (VI) para lograr un compuesto de fórmula (VII).

Un compuesto de fórmula (VIIa) puede usarse en la síntesis de un compuesto de fórmula (VIIIa):



donde R es como se definió arriba, usando el método descrito arriba para la conversión de un compuesto de fórmula (VI) para lograr un compuesto de fórmula (VIII).

Un compuesto de fórmula (VIIIa) puede usarse en la síntesis de un compuesto de fórmula (IXa):



donde R es como se definió arriba, usando el método descrito arriba para la conversión de un compuesto de fórmula (VII) para lograr un compuesto de fórmula (IX).

La sal R-(-)-ácido mandélico de un compuesto de fórmula (IXa) puede generarse usando el método descrito arriba para la generación de la sal de ácido mandélico de un compuesto de fórmula (IX).

Los compuestos novedosos forman un adicional aspecto de la invención. En un adicional aspecto la invención proporciona consecuentemente compuestos de fórmula (I), (Ia), (II), (III), (V), (Va), (VI), (VIa), (VII), (VIIa), (VIII), (VIIIa), (IX) y (IXa) como se definieron arriba.

Compuestos particularmente preferidos incluyen:

(1R, 2S, 5R)-2-isopropil-5-metilciclobexil trans-2-(3,4-difluorofenil) ciclo propano carboxilato;

(1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans- (1R, 2R)-2-(3,4-difluorofenil) ciclo propano carboxilato;

(1R, 2S, 5R)-2-isopropil-5-metilciclohexil (E)-3-(3,4-difluorofenil)-2-propenoato;

(E)-3-(3,4-difluorofenil)-2-ácido propenóico;

(E)-3-(3,4-difluorofenil)-2-cloruro propenóil;

trans-(1R, 2R)-2-(3,4-difluorofenil)ciclo propano ácido carboxílico;

trans-(1R, 2R)-2-(3,4-difluorofenil)ciclo propano cloruro carbonilo;

trans-(1R, 2R)-2-(3,4-difluorofenil)ciclo propano ázido carbonilo;

trans-(1R, 2S)-2-(3,4-difluorofenil) ciclo propil amina;

y trans-(1R, 2S)-2-(3,4-difluorofenil)ciclo propanaminio (2R)-2-hidroxi-2-fenil-etanoato

Ejemplos

La invención se ilustra mediante los siguientes ejemplos no limitativos.

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Ejemplo 1

Este ejemplo ilustra la preparación de (E)-3-(3,4-difluorofenil)-2-ácido propenóico

Una mezcla agitada de piridina (15,5 kg) y piperidina (0,72 kg) se calentaron a 90°C. Se agregó ácido malónico (17,6 kg), seguido por lenta adición durante 50 minutos, de 3,4-difluorobenzaldehído (12,0 kg). La mezcla de la reacción se agitó a 90°C durante adicionales 4 horas y 36 minutos. Se agregó agua (58,5 kg) y 32 litros de la mezcla de piridina/agua se destiló fuera del reactor bajo presión reducida. La mezcla de la reacción se acidificó a pH 1 con 37% de ácido clorhídrico (6,4 kg) durante un periodo de 40 minutos, luego se enfrió a 25°C con fuerte agitación. Los sólidos se recogieron por filtración, se lavaron dos veces con 1% de ácido clorhídrico (34,8 L por lavado), una vez con agua (61 L) y luego se licuó a completamente al través en el filtro. El producto se secó entonces bajo vacío a 40°C durante 24 horas y 40 minutos, logrando 13,7 kg del producto cristalino.

Ejemplo 2

Este ejemplo ilustra la preparación de (E)-3-(3,4-difluorofenil)-2-propenoil cloruro.

Una mezcla agitada de (E)-3-(3,4-difluorofenil)-2-ácido propenóico (8,2 kg), tolueno (7,4 kg) y piridina (0,18 kg) se calentó a 65°C y luego se agregó cloruro de tionil (7,4 kg) durante 30 minutos. La reacción se agitó durante adicionales 2 horas 15 minutos después de que se completó la adición, luego se diluyó con tolueno (8,7 kg). El exceso de cloruro de tionil, dióxido de azufre y cloruro de hidrógeno se destiló entonces fuera conjuntamente con tolueno (10 L), bajo presión reducida, logrando una

solución del (E)-3-(3,4-difluorofenil)-2-cloruro propenoil en tolueno (aproximadamente 9 kg).

Ejemplo 3

Este ejemplo ilustra la preparación de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil (E)-3-(3,4-difluorofenil)-2-propenoato.

Una solución de L-mentol (7,1 kg) en tolueno (8,5 kg) se agregó durante un periodo de 20 minutos a la solución de (E)-3-(3,4-difluorofenil)-2-cloruro de propenoil (preparado como en el Ejemplo 2) y piridina (0,18 kg, 2,28 mol) agitando a 65°C. La mezcla de la reacción se agitó a 65°C durante adicionales 4 horas y 40 minutos después de que se completó la adición, luego se enfrió a 25°C y se agitó durante 14 horas. La solución se diluyó con tolueno (16 kg), se lavó con 5% de cloruro de sodio acuoso (6,4 kg), luego 6% de carbonato de hidrógeno de sodio (6,47 kg), luego agua (6,1 kg). La solución se secó azeotrópicamente por destilación del solvente (20 L) bajo presión reducida. Se agregó dimetil sulfoxido (33,9 kg) y el tolueno restante se sacó por destilación bajo presión reducida, logrando 47,3 kg de una solución de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil (E)-3-(3,4-difluorofenil)-2-propenoato (aproximadamente 13,3 kg) en dimetil sulfoxido.

Ejemplo 4.

Este ejemplo ilustra un método de preparar dimetilsulfoxonio metilida (dimetil(metileno)oxo- λ^6 -sulfano).

Polvo de hidróxido de sodio (1,2 kg), preparado moliendo tabletas de hidróxido de sodio en un molino rotativo a través de un tamiz de metal de 1 mm, e yoduro trimetilsulfoxonio (6,2 kg) se agitaron en dimetil sulfoxido

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(25,2 kg) bajo una atmósfera de nitrógeno a 25°C durante 90 minutos. La solución se usó directamente en la preparación de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-2-(3,4-difluorofenil) ciclo propano carboxilato.

Ejemplo 5

Este ejemplo ilustra un método de preparar dimetilsulfonio metilida (dimetil(metileno)-λ⁴-sulfano).

Polvo de hidróxido de sodio (970 mg), preparado moliendo tabletas de hidróxido de sodio en un molino rotativo a través de un tamiz de metal de 1 mm, e ioduro de trimetilsulfonio (4,66 g) se agitó en dimetilsulfóxido (17 ml) bajo una atmósfera de nitrógeno a 20 a 25°C durante 10 minutos. La solución se usó directamente en la preparación de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-2-(3,4-difluorofenil) ciclo propano carboxilato.

Ejemplo 6.

Este ejemplo ilustra la preparación de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-2-(3,4-difluorofenil)ciclo propano carboxilato

Una solución de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil 3,4-difluorofenil)-2-propenoato (aproximadamente 8,6 kg) en dimetil sulfóxido (aproximadamente 27,9 kg) se agregó con agitación durante 20 minutos a una mezcla de dimetilsulfonio metilida (aproximadamente 2,6 kg, preparado como se describió arriba), ioduro de sodio ((E)-3- (aproximadamente 4,2 kg), agua (aproximadamente 500 g) e hidróxido de sodio (aproximadamente 56 g) en dimetilsulfóxido (27,7 kg) a 25°C. La mezcla de la reacción se agitó durante adicionales 2 horas y 50 minutos a

25°C, luego se usó directamente para la preparación de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano carboxilato.

Ejemplo 7

Este ejemplo ilustra la preparación de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano carboxilato

Una solución cruda de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-2-(3,4-difluorofenil)ciclo propano carboxilato producida como se describió en el ejemplo 6 se calentó desde 25°C a 50°C durante un periodo de 1 hora y la temperatura se mantuvo durante una hora adicional. La mezcla se enfrió entonces con agitación desde 50°C a 35°C durante 4 horas, se mantuvo a 35°C durante 1 hora, luego se enfrió a 26°C durante 4 horas, se mantuvo a 26°C durante 1 hora, luego se enfrió a 19°C durante 3 horas y se mantuvo a 19°C durante 5 horas y 10 minutos. El producto cristalizó y se recogió por filtración, logrando un sólido cristalino (2,7 kg) el cual muestra que contiene una mezcla de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-(1R, 2R)-2-(3,4-difluorofenil)ciclo propano carboxilato (1,99 kg) y (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-(1S, 2S)-2-(3,4-difluorofenil)ciclo propano carboxilato (85 g).

Ejemplo 8

Este ejemplo ilustra un método alternativo de preparar (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano carboxilato

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n-Heptano (82,5 L) se destiló bajo presión reducida a partir de una solución de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-2-(3,4-difluorofenil) ciclo propano carboxilato (14m3 kg, 44m4 mol) en heptano (128,6 L). La mezcla se enfrió entonces de 34°C a 24°C durante un periodo de 3 horas y 20 minutos. Los cristales cultivados de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano carboxilato se agregaron entonces y la mezcla se enfrió a 0°C durante un periodo de 5 horas y 50 minutos. La filtración dio el producto como un sólido húmedo solvente cristalino (7,05 kg) el cual mostró que contenía una mezcla de (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano carboxilato (4,7 kg) y (1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-(1S, 2S)-2-(3,4-difluorofenil) ciclo propano carboxilato (1,1 kg).

Ejemplo 9

Este ejemplo ilustra un método de preparar trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano ácido carboxílico

(1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano carboxilato (9,6 kg, 91,8% de exceso diastereomérico) se disolvió en etanol (13,8 kg) y calentó con agitación a 46°C. 45% de hidróxido de sodio acuoso (3,1 kg) se agregó durante un periodo de 20 minutos y la mezcla se agitó durante adicionales 2 horas y 27 minutos. El solvente (28 L) se destiló sacándolo de la mezcla bajo presión reducida, luego la mezcla se enfrió a 24°C y se diluyó con agua (29,3 kg), después de lo cual el mentol liberado se extrajo en tolueno (3 lavadas cada una de 3,3 kg).

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El material acuoso restante se acidificó a pH 2 con 37% de ácido clorhídrico (3,3 L) y el producto se extrajo en tolueno (8,6 kg, luego 2 lavadas más de 4,2 kg y 4,3 kg). Los extractos de tolueno combinados se lavaron con 1% de ácido clorhídrico (4,9 L), luego se diluyó con tolueno adicional (4,2 kg) y secó azeotrópicamente por destilación del solvente (25 L) bajo presión reducida. Una dilución final con tolueno (24,2kg) se siguió por destilación del solvente bajo presión reducida (10 L) logrando una solución que contiene trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano ácido carboxílico (aproximadamente 3,45 kg) adecuado para la producción de trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano cloruro carbonilo.

Ejemplo 10.

Este ejemplo ilustra un método de preparar trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano cloruro carbonilo.

Piridina (70 ml) se agregó a una solución de trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano ácido carboxílico (aproximadamente 3,45 kg) en tolueno (aproximadamente 12,15 kg) preparado como se describió arriba, y la mezcla se calentó luego a 65°C. Cloruro de tionil (2,3 kg) se agregó durante un periodo de 1 hora y la mezcla se agitó a 70°C durante 3 horas. Se agregó cloruro de tionil (0,5 kg) y la mezcla se agitó adicionales 2 horas a 70°C. Una alícuota final de cloruro tionil (0,5 kg) se agregó y la mezcla de la reacción se agitó durante 1 hora a 70°C, luego se enfrió a 40°C. Periódicas adiciones de tolueno (45 kg, 3 adiciones de 15 kg cada una) se hicieron durante la destilación del solvente (aproximadamente 60 L) de la mezcla bajo presión reducida, luego la solución de trans-(1R, 2R)-2-(3-4-difluorofenil) ciclo propano cloruro carbonilo (1,8 kg aproximadamente) en tolueno (aproximadamente 6 a 9 L) se enfrió a 20°C.

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Ejemplo 11

Este ejemplo ilustra un método de preparar trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano ázido carbonilo.

Una solución de trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano cloruro carbonilo (aproximadamente 3,8 kg) en tolueno (aproximadamente 6 - 9 L) a 1°C se agregó durante un periodo de 74 minutos a una mezcla de ázido de sodio (1,24 kg), tetrabutilamonio bromuro (56 g) y carbonato de sodio (922 g) en agua (6,2 kg), agitando a 1,5°C. La mezcla se agitó a 0°C durante 1 hora y 55 minutos, luego la capa acuosa se diluyó con agua fría (3,8 kg), se agitó brevemente, luego se separó. La capa de tolueno se lavó una vez más a 0°C con agua (3,8 kg), luego con 20% cloruro de sodio acuoso (3,8 L), luego se almacenó a 3°C para adicional uso.

Ejemplo 12.

Este ejemplo ilustra un método de preparar trans-(2R, 2S)-2-(3,4-difluorofenil) ciclo propilamina.

Una solución fría de trans-(1R, 2R)-2-(3,4- difluorofenil) ciclo propano ázido carbonilo preparado como se describió en el Ejemplo 11 se agregó durante un periodo de 41 minutos a tolueno (6,0 kg) agitando a 100°C. La mezcla se agitó, durante adicionales 55 minutos a 100°C, luego se enfrió a 20°C y se agregó durante un periodo de 2 horas y 15 minutos a ácido clorhídrico (3M, 18,2 kg) agitando a 80°C. Después de 65 minutos la solución se diluyó con agua (34 kg) y enfrió a 25°C. La capa de tolueno se retiró y la capa acuosa se basificó a pH 12 con 45% de hidróxido de sodio (3,8 kg) y el producto se extrajo entonces en acetato de etilo (31 kg) y se lavó dos veces con agua (13,7 kg por lavada), logrando una solución que

contiene trans-(1R, 2S)-2-(3,4-difluorofenil) ciclo propilamina (2,6 kg, 91,8% de exceso enantiomérico) en acetato de etilo (29,5 L).

Ejemplo 13

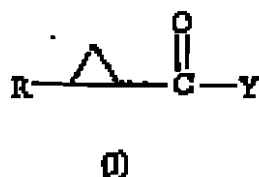
Este ejemplo ilustra un método de preparar trans-(1R, 2S)-2-(3,4-difluorofenil) ciclo propanaminio (2R)-2-hidroxi-2-feniletanoato.

R-(-)-ácido mandélico (2,26 kg) se agregó a una solución que contiene trans-(1R, 2S)-2-(3,4-difluorofenil) ciclo propilamina (2,6 kg, 91,8% de exceso enantiomérico), agitando a 17°C en acetato de etilo (45,3 L). La mezcla se agitó a 25°C durante 3 horas y 8 minutos, luego se filtró y lavó dos veces con acetato de etilo (13,8 kg total). El producto cristalino se secó a 40°C bajo presión reducida durante 21 horas, logrando trans-(1R, 2S)-2-(3,4-difluorofenil) ciclo propanaminio (2R)-2-hidroxi-2-feniletanoato (4 a 45 kg).

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REIVINDICACIONES

1. Un proceso para la preparación de un compuesto de fórmula (I):

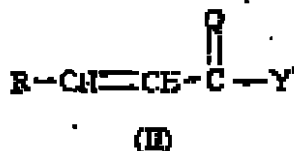


donde:

R es fenil sustituido con uno o más halógenos;

Y es OR¹ donde R es un alquil de cadena recta, alquil ramificado, cicloalquil, o un grupo bicicloheptil sustituido;

que comprende contactar un compuesto de fórmula (II):



donde R e Y son como se definió arriba, con dimetilsulfoxonio metilida en presencia de un solvente a una temperatura de -10°C - 90°C.

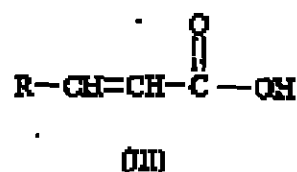
2. Un proceso para la preparación de un compuesto de fórmula (I) como se reivindicó en la reivindicación 1 que comprende los pasos de:

- i) reaccionar una sal trimetilsulfoxonio con un hidróxido de metal sólido en dimetil sulfóxido a temperatura ambiente o elevada para producir dimetilsulfoxonio metilida; y
- ii) contactar el compuesto de fórmula (II) con dimetilsulfoxonio metilida en presencia de un solvente a una temperatura de -10°C - 90°C.

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3. Un proceso de acuerdo con la reivindicación 2 donde el hidróxido de metal es hidróxido de sodio.

4. Un proceso de acuerdo con una cualquiera de las reivindicaciones precedentes donde el compuesto de fórmula (II) se prepara a partir de un compuesto de fórmula (III):

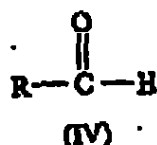


donde R es como se definió en la reivindicación 1, mediante la reacción con un agente de clorinación en presencia de un solvente inerte y un catalizador a una temperatura de 0-200°C, y luego reaccionando la solución resultante con YH o Y⁻, donde Y es como se definió en la reivindicación 1, a una temperatura elevada.

5. Un proceso de acuerdo con la reivindicación 4 donde un compuesto de fórmula (III) se reacciona con cloruro de tionil en presencia de un solvente inerte y piridina a una temperatura de 0-200°C, y la solución resultante se reacciona luego con YH o Y⁻, donde Y es como se definió en la reivindicación 1, a una temperatura elevada.

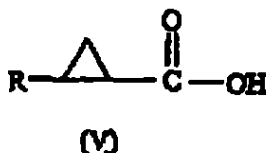
6. Un proceso de acuerdo con una cualquiera de las reivindicaciones precedentes donde YH representa L-mentol.

7. Un proceso de acuerdo con una cualquiera de las reivindicaciones 4 a 6 donde un compuesto de fórmula (III) se prepara contactando un compuesto de fórmula (IV):



donde R es como se definió en la reivindicación 1, con ácido malónico en presencia de piridina y piperidina a temperaturas elevadas.

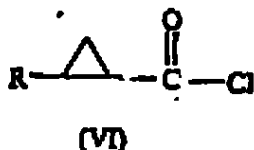
8. Un proceso para la preparación de un compuesto de fórmula (V):



donde R es como se definió en la reivindicación 1, que comprende la hidrólisis de base de un compuesto de fórmula (I).

9. Un proceso de acuerdo con la reivindicación 8 donde la hidrólisis de base se logra usando un hidróxido de metal alcalino y solvente a 10 – 100°C.

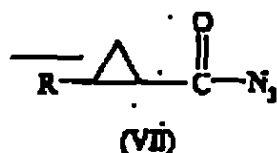
10. Un proceso para la preparación de un compuesto de fórmula (VI):



donde R es como se definió en la reivindicación 1, a partir de un compuesto de fórmula (V) mediante la reacción con cloruro de tionil en presencia de solvente y un catalizador a 0-200°C.

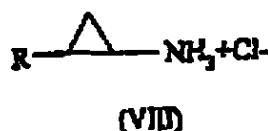
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11. Un proceso para la preparación de un compuesto de fórmula (VII):



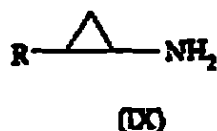
donde R es como se definió en la reivindicación 1, a partir de un compuesto de fórmula (VI), mediante la reacción con un ázido de metal alcalino en presencia de un catalizador de transferencia de fase, carbonato de potasio acuoso y un solvente inerte.

12. Un proceso para la preparación de un compuesto de fórmula (VIII):



donde R es como se definió en la reivindicación 1, a partir de un compuesto de fórmula (VII), mediante el arreglo en tolueno a temperaturas elevadas, y la subsecuente reacción con ácido clorhídrico a temperaturas elevadas.

13. Un proceso para la preparación de un compuesto de fórmula (IX):



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donde R es como se definió en la reivindicación 1, ajustando a pH 10 o más una solución acuosa de la sal de un compuesto de fórmula (VIII).

14. Un proceso para la preparación de un compuesto la sal de ácido mandélico de un compuesto de fórmula (IX) mediante la adición de R-(-)-ácido mandélico al compuesto de fórmula (IX) se hace en la reivindicación 13, a temperatura ambiente o temperatura elevada.

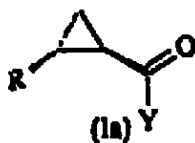
15. Un proceso de acuerdo con una cualquiera de las reivindicaciones precedentes donde R es fenil sustituido por uno o más átomos de flúor.

16. Un proceso de acuerdo con la reivindicación 15 donde R es 3,4-difluorofenil.

17. un proceso de acuerdo con una cualquiera de las reivindicaciones precedentes donde Y es chiral.

18. Un proceso de acuerdo con la reivindicación 17 donde Y es L-mentoxi.

19. Un proceso de acuerdo con una cualquiera de las reivindicaciones 1 a 18 donde un compuesto de fórmula (1) se resuelve para lograr un compuesto de fórmula (1a):



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donde R e Y son como se definió en la reivindicación 1, mediante cristalización o mediante métodos cromatográficos.

20. Un proceso de acuerdo con la reivindicación 19 donde la resolución se lleva a cabo extractando un compuesto de fórmula (I) en heptano y luego efectuando la cristalización a partir de extractos de heptano.

21. Los compuestos intermediarios de las fórmulas (I), (Ia), (II), (III), (V), (Va), (VI), (VIa), (VII), (VIIa), (VIII), (VIIIa), (IX) y (IXa) anteriores.

22. Los compuestos intermediarios:

(1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-2-(3,4-difluorofenil) ciclo propano carboxilato,

(1R, 2S, 5R)-2-isopropil-5-metilciclohexil trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano carboxilato;

(1R, 2S, 5R)-2-isopropil-5-metilciclohexil (E)-3-(3,4-difluorofenil)-2-propenoato;

(E)-3-(3,4-difluorofenil)-L-ácido propenóico,

(E)-3-(3,4-difluorofenil)-2-cloruro propenol;

trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano ácido carboxílico;

trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano cloruro carbonilo;

trans-(1R, 2R)-2-(3,4-difluorofenil) ciclo propano azido carbonilo;

trans-(1R, 2E)-2-(3,4-difluorofenil) ciclo propilamina; y

trans-(1R, 2S)-2-(3,4-difluorofenil) ciclo propanaminio (2R)-2-hidroxi-2-feniletanoato.

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(54) TITLE: PROCESS FOR THE PREPARATION OF CYCLOPROPYL CARBOXYLIC ACID ESTERS AND DERIVATIVES

(57) Abstract: The invention relates to a novel process for the preparation of certain cyclopropyl carboxylic acid esters and other cyclopropyl carboxylic acid derivatives; a novel process for the preparation of dimethylsulfoxonium methylide and dimethylsulfonium methylide; to the use of certain cyclopropyl carboxylic acid esters in a process for the preparation of intermediates that can be used in the synthesis of pharmaceutically active compounds, and to certain intermediates provided by these processes.

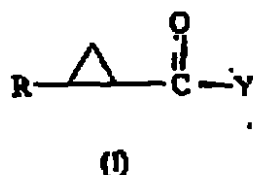
PROCESS FOR THE PREPARATION OF CYCLOPROPYL CARBOXYLIC ACID ESTERS AND DERIVATIVES

FIELD OF THE INVENTION

The present invention relates to a novel process for the preparation of certain cyclopropyl carboxylic acid esters and other cyclopropyl carboxylic acid derivatives; a novel process for the preparation of dimethylsulfoxonium methylide and dimethylsulfonium methylide; to the use of certain cyclopropyl carboxylic acid esters in a process for the preparation of intermediates that can be used in the synthesis of pharmaceutically active entities, and to certain intermediates provided by these processes.

DESCRIPTION OF THE INVENTION

In a first aspect the invention therefore provides a process for the preparation of a compound of formula (I):

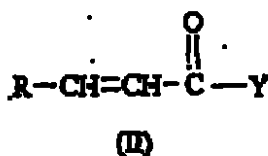


wherein:

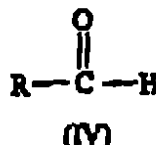
R is phenyl substituted with one or more halogen;

Y is OR^1 , where R^1 is a straight chain alkyl, branched alkyl, cycloalkyl, or a substituted bicycloheptyl group (eg bornyl).

which comprises contacting a compound of formula (II):

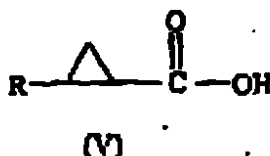


where R and Y are as defined above, with dimethylsulfoxonium methylide in the presence of a solvent.



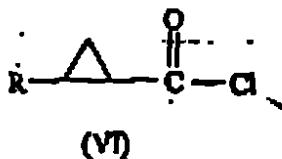
where R is as defined above, with malonic acid in the presence of pyridine and piperidine at an elevated temperature, preferably 50-90°C.

A compound of formula (I) can be hydrolysed using basic hydrolysis to yield a compound of formula (V):



where R is as defined above. For example, ester groups are preferably removed by basic hydrolysis using an alkali metal hydroxide, such as sodium hydroxide or lithium hydroxide, or quaternary ammonium hydroxide in a solvent, such as water, an aqueous alcohol or aqueous tetrahydrofuran, at a temperature from 10 - 100°C. Most preferably the base is sodium hydroxide, the solvent is ethanol, and the reaction temperature is 50°C.

A compound of formula (V) can be used to generate a compound of formula (VI):



where R is as defined above, by reaction with thionyl chloride or another suitable chlorinating agent in the presence of toluene, or another suitable solvent, and an optional catalyst, preferably pyridine, at 0-200°C. Preferably the temperature is 65-70°C.

A compound of formula (VI) can be used in the synthesis of a compound of formula (VII):

Suitably the solvent is a polar solvent, preferably dimethyl sulfoxide. Suitably, the reaction is carried out at -10°C - 90°C , preferably 25°C .

The dimethylsulfoxonium methylide can be prepared by reacting a trimethylsulfoxonium salt with a solid strong base, preferably in solid form, in dimethyl sulfoxide at ambient or an elevated temperature. Suitably, the base is a metal hydroxide, eg NaOH, LiOH, or alkali metal hydride, eg NaH. Preferably the base is sodium hydroxide.

Preferably, trimethylsulfoxonium iodide is stirred with sodium hydroxide powder in dimethyl sulfoxide (in the absence of a phase transfer catalyst), optionally under nitrogen, at $20-25^{\circ}\text{C}$ for 90 minutes. Alternatively, the dimethylsulfoxonium methylide can be prepared from a trimethylsulfoxonium salt (preferably iodide or chloride) using sodium hydroxide in dimethyl sulfoxide with a phase transfer catalyst, for example tetrabutyl-ammonium bromide, or with other strong bases, such as alkali metal hydrides, in dimethyl sulfoxide.

A compound of formula (II) can be prepared by reacting a compound of formula (III):



(II)

where R is as defined above, with a suitable chlorinating agent in the presence of an inert solvent and an optional catalyst at a temperature of $0-200^{\circ}\text{C}$. Preferably Y is OR¹, the chlorinating agent is thionyl chloride, the inert solvent is toluene, and the catalyst is pyridine. Suitably the reaction temperature is 70°C . The resulting acid chloride is then reacted with YH or Y⁻, (where Y⁻ is an anionic species of Y), Y is as defined above, optionally at an elevated temperature, such as 100°C .

A compound of formula (III) can be prepared using standard chemistry, for example by contacting a compound of formula (IV):

1 salt of a compound of formula (IX) can be generated by addition of *R*-(*-*)-mandelic acid at ambient or an elevated temperature to a solution of a compound of formula (IX) in a solvent, preferably ethyl acetate. Preferably the temperature is 20°C.

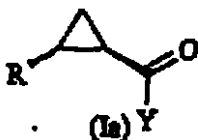
- 3 Suitably *R* is phenyl optionally substituted by one or more halogen atoms. Preferably, *R* is phenyl substituted by one or more fluorine atoms. More preferably *R* is 4-fluorophenyl or 3,4-difluorophenyl.

Preferably *Y* is *D*-menthoxy, or more preferably, *L*-menthoxy.

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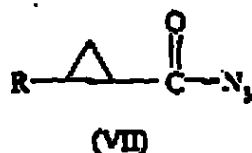
Compounds of formulae (I) to (IX) can exist in different isomeric forms (such as *cis/trans*, enantiomers, or diastereoisomers). The process of this invention includes all such isomeric forms and mixtures thereof in all proportions.

- 15 Where *Y* is chiral, a compound of formula (I) will be a mixture of diastereoisomers and can be resolved to yield a diastereomerically-enriched compound of formula (Ia):



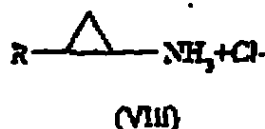
where *R* and *Y* are as defined above, by crystallisation or by chromatographic methods.

- Preferably the crystallisation is carried out *in situ* following the synthesis of a compound of formula (I), as described above, by heating the crude reaction mixture until total or near-total dissolution is achieved, then cooling at an appropriate rate until sufficient crystals of the desired quality are formed. The crystals are then collected by filtration. Alternatively, the resolution can be carried out in any other suitable solvent, such as a hydrocarbon, eg heptane by extracting a compound of formula (I) into a suitable amount of the solvent, heating the extracts until total dissolution is achieved, then cooling at an appropriate rate until sufficient crystals of the desired quality are formed. Optionally the organic extracts can be washed with water, dried over magnesium sulfate and filtered prior to the crystallisation described above.



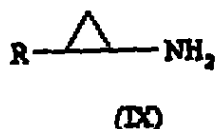
where R is as defined above, by reacting with an alkali metal azide (preferably sodium azide) in the presence of a phase transfer catalyst (preferably tetra-*n*-butylammonium bromide), aqueous potassium carbonate and an inert solvent (preferably toluene). Preferably the reaction temperature is 0 - 10°C.

A compound of formula (VII) can be used in the synthesis of a compound of formula (VIII):

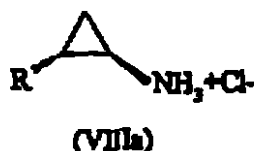


where R is as defined above, by rearrangement in toluene at temperatures between 0°C and 200°C, preferably at a reaction temperature of 90-100°C, after which the isocyanate intermediate is reacted with hydrochloric acid at elevated temperatures, preferably 85-90°C.

An unprotonated parent amine (free base) of formula (IX):

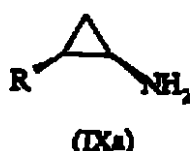


where R is as defined above, can be liberated by adjusting the pH of an aqueous solution of the salt of a compound of formula (VIII) to 10 or more. This can then be converted to other salts of organic acids or inorganic acids, preferably mandelic acid. The *R*-(-)-mandelic acid



where R is as defined above, using the method described above for the conversion of a compound of formula (VII) to yield a compound of formula (VIII).

- 3 A compound of formula (VIIa) can be used in the synthesis of a compound of formula (IXa):



where R is as defined above, using the method described above for the conversion of a compound of formula (VIII) to yield a compound of formula (IX).

10

The *R*-(-)-mandelic acid salt of a compound of formula (IXa) can be generated using the method described above for the generation of the mandelic acid salt of a compound of formula (IX).

15

Novel compounds form a further aspect of the invention. In a further aspect the invention therefore provides compounds of formula (I), (Ia), (II), (III), (V), (Va), (VI), (VIa), (VII), (VIIa), (VIII), (VIIIa), (IX) and (IXa) as defined above.

Particularly preferred compounds include:

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(1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-2-(3,4-difluorophenyl)cyclopropanecarboxylate;

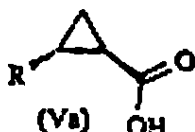
(1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropane carboxylate;

(1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl (E)-3-(3,4-difluorophenyl)-2-propenoate;

25

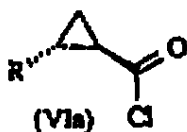
(E)-3-(3,4-difluorophenyl)-2-propenoic acid;

A compound of formula (Ia) can be hydrolysed to yield a compound of formula (Va):



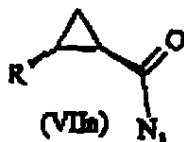
where R is as defined above, using the method described above for the hydrolysis of a compound of formula (I) to yield a compound of formula (V).

A compound of formula (Va) can be used to generate a compound of formula (Via):



where R is as defined above, using the method described above for the conversion of a compound of formula (V) to yield a compound of formula (VI).

A compound of formula (Via) can be used in the synthesis of a compound of formula (VIIa):



where R is as defined above, using the method described above for the conversion of a compound of formula (VI) to yield a compound of formula (VII).

A compound of formula (VIIa) can be used in the synthesis of a compound of formula (VIIIa):

34
33

complete, then diluted with toluene (8.7kg). Excess thionyl chloride, sulfur dioxide and hydrogen chloride were then distilled out, together with toluene (10 L), under reduced pressure, yielding a solution of the (S)-3-(3,4-difluorophenyl)-2-propenoyl chloride (approximately 9 kg) in toluene.

Example 3.

This example illustrates the preparation of (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (S)-3-(3,4-difluorophenyl)-2-propenoate.

- 10 A solution of L-menthol (7.1kg) in toluene (8.5kg) was added over a 20 minute period to the solution of (E)-3-(3,4-difluorophenyl)-2-propenoyl chloride (prepared as in Example 2) and pyridine (0.18kg, 2.28 mol) stirring at 65°C. The reaction mixture was stirred at 65°C for a further 4 hours and 40 minutes after the addition was complete, then cooled to 25°C and stirred for a 14 hours. The solution was diluted with toluene (16kg), washed with 5% aqueous sodium chloride (6.4kg), then 6% sodium hydrogen carbonate (6.47kg), then water (6.1kg). The solution was dried azeotropically by distillation of the solvent (20 L) under reduced pressure. Dimethyl sulfoxide (33.9 kg) was added and the remaining toluene was distilled off under reduced pressure, affording 47.3kg of a solution of (1R,2S,5R)-2-isopropyl-5-methylcyclohexyl (E)-3-(3,4-difluorophenyl)-2-propenoate (approx. 13.3 kg) in dimethyl sulfoxide.
- 20

Example 4.

This example illustrates a method of preparing dimethylsulfoxonium methylide

(dimethyl(methylene)sulfoxide):

- 25 Sodium hydroxide powder (1.2kg), prepared by milling sodium hydroxide pellets in a rotary mill through a 1mm metal sieve, and trimethylsulfoxonium iodide (6.2kg) were stirred in dimethyl sulfoxide (25.2kg) under a nitrogen atmosphere at 25°C for 90 min. The solution was used directly in the preparation of (1R, 2S, 5R)-2-isopropyl-5-methylcyclohexyl *trans*-2-(3,4-difluorophenyl)cyclopropanecarboxylate.
- 30

Example 5.

- (*E*)-3-(3,4-difluorophenyl)-2-propenoyl chloride;
trans-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylic acid;
trans-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl chloride;
trans-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl azide;
5 *trans*-(1*R*, 2*S*)-2-(3,4-difluorophenyl) cyclopropyl amine;
and *trans*-(1*R*, 2*S*)-2-(3,4-difluorophenyl)cyclopropanaminium (2*R*)-2-hydroxy-2-phenylethanone

Examples

- x The invention is illustrated by the following non-limiting examples.

Example 1.

This example illustrates the preparation of (*E*)-3-(3,4-difluorophenyl)-2-propenoic acid

- 15 A stirred mixture of pyridine (15.5 kg) and piperidine (0.72 kg) were heated to 90°C. Malonic acid (17.6 kg) was added, followed by slow addition, over 50 minutes, of 3,4-difluorobenzaldehyde (12.0 kg). The reaction mixture was stirred at 90°C for a further 4 hours and 36 minutes. Water (58.5 kg) was added and 32 litres of the pyridine/water mixture then was distilled out of the reactor under reduced pressure. The reaction mixture
20 was acidified to pH 1 with 37% hydrochloric acid (6.4 kg) over a 40-minute period, then cooled to 25°C with strong stirring. The solids were collected by filtration, washed twice with 1 % hydrochloric acid (34.8 L per wash), once with water (61 L) and then deliquored thoroughly in the filter. The product was then dried under vacuum at 40°C for 24 hours and 40 minutes, affording 13.7 kg of the crystalline product.

Example 2.

This example illustrates the preparation of (*E*)-3-(3,4-difluorophenyl)-2-propenoyl chloride.

- 30 A stirred mixture of (*E*)-3-(3,4-difluorophenyl)-2-propenoic acid (8.2 kg), toluene (7.4kg) and pyridine (0.18kg) was heated to 65°C and then thionyl chloride (7.4kg) was added over 30 minutes. The reaction was stirred for a further 2h 15 minutes after the addition was

then cooled to 19°C over 3 hours and kept at 19°C for 5 hours and 10 minutes. The product crystallised and was collected by filtration, affording a crystalline solid (2.7 kg) which was shown to contain a mixture of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate (1.99 kg) and (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*S*,2*S*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate (85 g).

Example 8.

This example illustrates an alternative method of preparing (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate

10

n-Heptane (82.5 L) was distilled under reduced pressure from a solution of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-2-(3,4-difluorophenyl)cyclopropanecarboxylate (14.3 kg, 44.4 mol) in heptane (128.6 L). The mixture was then cooled from 34°C to 24°C over a period of 3 hours and 20 minutes. Seed crystals of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate were then added and the mixture was cooled to 0°C over a period of 5 hours and 50 minutes.

15

Filtration afforded the product as a crystalline solvent wet solid (7.05 kg) which was shown to contain a mixture of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate (4.7 kg) and (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*S*,2*S*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate (1.1 kg).

20

Example 9.

This example illustrates a method of preparing *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylic acid.

25

(1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate (9.6 kg, 91.8% diastereomeric excess) was dissolved in ethanol (13.8 kg) and heated with stirring to 46°C. 45% Aqueous sodium hydroxide (3.1 kg) was added over a 20 minute period and the mixture was stirred for a further 2 hours and 27 minutes. Solvent (28 L) was distilled out of the mixture under reduced pressure, then the mixture was cooled to 24°C and diluted with water (29.3 kg), after which the liberated menthol was extracted into toluene (3 washes of 3.3 kg each).

30

This example illustrates a method of preparing dimethylsulfoxium methylide (dimethyl(methylene)- λ^4 -sulfane).

Sodium hydroxide powder (970mg), prepared by milling sodium hydroxide pellets in a rotary mill through a 1mm metal sieve, and trimethylsulfoxium iodide (4.66 g) were stirred in dimethyl sulfoxide (17 ml) under a nitrogen atmosphere at 20-25°C for 10 min. The solution was used directly in the preparation of (1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-2-(3,4-difluorophenyl)cyclopropanecarboxylate.

10 Example 6.

This example illustrates the preparation of (1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-2-(3,4-difluorophenyl)cyclopropanecarboxylate

A solution of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl 3,4-difluorophenyl-2-propenoate (approximately 8.6 kg) in dimethyl sulfoxide (approximately 27.9 kg) was added with stirring over 20 minutes to a mixture of dimethylsulfoxium methylide (approximately 2.6kg, prepared as described above), sodium iodide ((*E*)-3 (approximately 4.2 kg), water (approximately 500 g) and sodium hydroxide (approximately 56 g) in dimethylsulfoxide (27.7 kg) at 25°C. The reaction mixture was stirred for a further 2 hours and 50 minutes at 25°C, then used directly for the preparation of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate.

Example 7.

This example illustrates the preparation of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylate

A crude solution of (1*R*, 2*S*, 5*R*)-2-isopropyl-5-methylcyclohexyl *trans*-2-(3,4-difluorophenyl)cyclopropanecarboxylate produced as described in example 6 was heated with stirring from 25°C to 50°C over a 1 hour period and the temperature was maintained for a further hour. The mixture was then cooled with stirring from 50°C to 35°C over 4 hours, kept at 35°C for 1 hour, then cooled to 26°C over 4 hours, kept at 26°C for 1 hour,

The remaining aqueous material was acidified to pH 2 with 37% hydrochloric acid (3.3 L) and the product was extracted into toluene (8.6 kg, then 2 more washes of 4.2 kg and 4.3 kg). The combined toluene extracts were washed with 1% hydrochloric acid (4.9 L), then diluted with further toluene (4.2 kg) and azeotropically dried by distillation of the solvent (25 L) under reduced pressure. A final dilution with toluene (24.2 kg) was followed by distillation of the solvent under reduced pressure (10 L) affording a solution containing *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylic acid (approximately 3.45 kg) suitable for the production of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl chloride.

Example 10.

This example illustrates a method of preparing *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl chloride.

Pyridine (70 ml) was added to a solution of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarboxylic acid (approximately 3.45 kg) in toluene (approximately 12 - 15 kg) prepared as described above, and the mixture was then heated to 65°C. Thionyl chloride (2.3 kg) was added over a period of 1 hour and the mixture was stirred at 70°C for 3 hours. Thionyl chloride (0.5 kg) was added and the mixture was stirred a further 2 hours at 70°C. A final aliquot of thionyl chloride (0.5 kg) was added and the reaction mixture was stirred for 1 hour at 70°C, then cooled to 40°C. Periodic additions of toluene (45 kg, 3 additions of 15 kg each) were made during distillation of solvent (approximately 60 L) from the mixture under reduced pressure, then the solution of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl chloride (approximately 3.8 kg) in toluene (approximately 6 - 9 L) was cooled to 20°C.

Example 11.

This example illustrates a method of preparing *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl azide.

A solution of *trans*-(1*R*, 2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl chloride (approximately 3.8 kg) in toluene (approximately 6 - 9 L) at 1°C was added over a period

of 74 minutes to a mixture of sodium azide (1.24 kg), tetrabutylammonium bromide (56 g) and sodium carbonate (922 g) in water (6.2 kg), stirring at 1.5°C. The mixture was stirred at 0°C for 1 hour and 55 minutes, then the aqueous layer was diluted with cold water (3.8 kg), stirred briefly, then separated. The toluene layer was washed once more at 0°C with water (3.8 kg), then with 20% aqueous sodium chloride (3.8 L), then stored at 3°C for further use.

Example 12.

This example illustrates a method of preparing *trans*-(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropylamine.

A cold solution of *trans*-(1*R*,2*R*)-2-(3,4-difluorophenyl)cyclopropanecarbonyl azide prepared as described in Example 11 was added over a period of 41 minutes to toluene (6.0 kg) stirring at 100°C. The mixture was stirred for a further 55 minutes at 100°C, then cooled to 20°C and added over a period of 2 hours and 15 minutes to hydrochloric acid (3*M*, 18.2 kg) stirring at 80°C. After 65 minutes the solution was diluted with water (34 kg) and cooled to 25°C. The toluene layer was removed and the aqueous layer was basified to pH 12 with 45% sodium hydroxide (3.8 kg) and the product was then extracted into ethyl acetate (31 kg) and washed twice with water (13.7 kg per wash), affording a solution containing *trans*-(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropylamine (2.6 kg, 91.8% enantiomeric excess) in ethyl acetate (29.5 L).

Example 13.

This example illustrates a method of preparing *trans*-(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanaminium (2*R*)-2-hydroxy-2-phenylacetate.

R-(-)-Mandelic acid (2.26 kg) was added to a solution containing *trans*-(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropylamine (2.6 kg, 91.8% enantiomeric excess), stirring at 17°C in ethyl acetate (45.3 L). The mixture was stirred at 25°C for 3 hours and 8 minutes, then filtered and washed twice with ethyl acetate (13.8 kg total). The crystalline product was dried at 40°C under reduced pressure for 22 hours, affording *trans*-(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropanaminium (2*R*)-2-hydroxy-2-phenylacetate (4.45 kg).

Claims

1. A process for the preparation of a compound of formula (I):



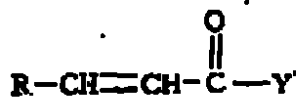
(I)

wherein:

R is phenyl substituted with one or more halogen;

Y is OR^1 , where R^1 is a straight chain alkyl, branched alkyl, cycloalkyl, or a substituted bicycloheptyl group;

which comprises contacting a compound of formula (II):



(II)

where R and Y are as defined above, with dimethylsulfoxonium methylide in the presence of a solvent at a temperature of -10°C - 90°C .

2. A process for the preparation of a compound of formula (I) as claimed in claim 1 comprising the steps of;

- i) reacting a trialkylsulfoxonium salt with a solid metal hydroxide in dimethyl sulfoxide at ambient or an elevated temperature to produce dimethylsulfoxonium methylide; and
- ii) contacting compound of formula (II) with dimethylsulfoxonium methylide in the presence of a solvent at a temperature of -10°C - 90°C .

3. A process according to claim 2 in which the metal hydroxide is sodium hydroxide.

4. A process according to any one of the preceding claims in which the compound of formula (II) is prepared from a compound of formula (III):



(III)

where R is as defined in claim 1, by reaction with a chlorinating agent in the presence of an inert solvent and a catalyst at a temperature of 0-200°C, and then reacting the resulting solution with YH or Y', where Y is as defined in claim 1, at an elevated temperature.

5. A process according to claim 4 in which a compound of formula (III) is reacted with thionyl chloride in the presence of an inert solvent and pyridine at a temperature of 0-200°C, and the resulting solution is then reacted with YH or Y', where Y is as defined in claim 1, at an elevated temperature.

6. A process according to any one of the preceding claims in which YH represents L-menthol.

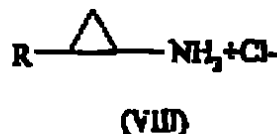
7. A process according to any one of claims 4 to 6 in which a compound of formula (III) is prepared by contacting a compound of formula (IV):



(IV)

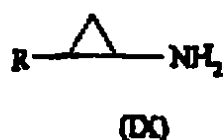
where R is as defined in claim 1, with malonic acid in the presence of pyridine and piperidine at elevated temperatures.

8. A process for the preparation of a compound of formula (V):



where R is as defined in claim 1, from a compound of formula (VII), by rearrangement in toluene at elevated temperatures, and subsequent reaction with hydrochloric acid at elevated temperatures.

13. A process for the preparation of a compound of formula (IX):



14. where R is as defined in claim 1, by adjusting to pH 10 or more an aqueous solution of the salt of a compound of formula (VIII).

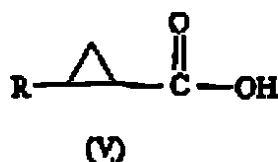
15. A process for the preparation of a compound the mandelic acid salt of a compound of formula (IX) by addition of R-(-)-mandelic acid to the compound of formula (IX) as made in claim 13, at ambient or an elevated temperature.

16. A process according to any one of the preceding claims in which R is phenyl substituted by one or more fluorine atoms.

17. A process according to claim 15 in which R is 3,4-difluorophenyl.

18. A process according to any one of the preceding claims in which Y is chiral

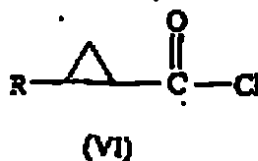
19. A process according to claim 17 in which Y is L-menthonyl.



where R is as defined in claim 1, comprising base hydrolysis of a compound of formula (I).

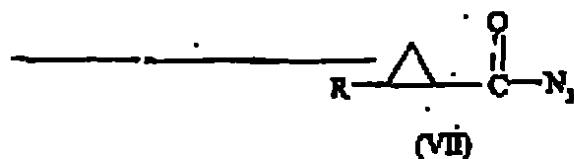
9. A process according to claim 8 wherein base hydrolysis is achieved using an alkali metal hydroxide and solvent at 10 - 100°C.

10. A process for the preparation of a compound of formula (VI):



where R is as defined in claim 1, from a compound of formula (V) by reaction with thionyl chloride in the presence of solvent and a catalyst at 0-200°C.

11. A process for the preparation of a compound of formula (VII):

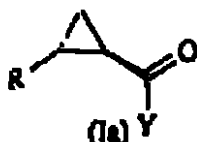


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where R is as defined in claim 1, from a compound of formula (VI), by reaction with an alkali metal azide in the presence of a phase transfer catalyst, aqueous potassium carbonate and an inert solvent.

20 12. A process for the preparation of a compound of formula (VIII):

19. A process according to any one of claims 1 to 18 in which a compound of formula (I) is resolved to yield a compound of formula (Ia):



20. where R and Y are as defined in claim 1, by crystallisation or by chromatographic methods

21. A process according to claim 19 in which the resolution is carried out by extracting a compound of formula (I) into heptane and then effecting crystallisation from the heptane extracts.

22. The intermediate compounds of formulae (I), (Ia), (II), (III), (V), (Va), (VI), (VIa), (VII), (VIIa), (VIII), (VIIIa), (IX) and (IXa) above.

23. The intermediate compounds:

- (1R, 2S, 5R)-2-isopropyl-5-methylcyclohexyl *trans*-2-(3,4-difluorophenyl)cyclopropanecarboxylate;
- (1R, 2S, 5R)-2-isopropyl-5-methylcyclohexyl *trans*-(1R, 2R)-2-(3,4-difluorophenyl)cyclopropane carboxylate;
- (1R, 2S, 5R)-2-isopropyl-5-methylcyclohexyl (*E*)-3-(3,4-difluorophenyl)-2-propenoate;
- (*E*)-3-(3,4-difluorophenyl)-2-propenoic acid;
- (*E*)-3-(3,4-difluorophenyl)-2-propenoyl chloride;
- trans*-(1R, 2R)-2-(3,4-difluorophenyl)cyclopropanecarboxylic acid;
- trans*-(1R, 2R)-2-(3,4-difluorophenyl)cyclopropanecarbonyl chloride;
- trans*-(1R, 2R)-2-(3,4-difluorophenyl)cyclopropanecarbonyl azide;
- trans*-(1R, 2S)-2-(3,4-difluorophenyl) cyclopropyl amine;
- and *trans*-(1R, 2S)-2-(3,4-difluorophenyl)cyclopropanaminium (2R)-2-hydroxy-2-phenylethanoate

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/01240

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07C 67/347, C07C 69/003, C07C 69/017, C07C 69/743, C07C 69/753,
C07C 61/04, C07C 69/96, C07C 233/58

According to International Patent Classification (IPC) or to any other classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,OK,FI,NO classes as above

Keywords have been considered during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Journal of the American chemical society, Volume 87, 1965, E. J. Corey et al, "Dimethyloxosulfonium Methylide ((CH ₃) ₂ SOCH ₂) and Dimethylsulfonium Methylide ((CH ₃) ₂ SCH ₂). Formation and Application to Organic Synthesis" page 1353 - page 1364	1-3,15-20
X	Advanced Organic Chemistry, Fourth Edition, Jerry March, "Reactions, Mechanisms, and structure, John Wiley & Sons, New York, 1992, pages 872, 741	1-3,15-20
X	pages 428-429	11,15-20
X	pages 1091-1095	12,15-20

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents

"A" documents defining by general state of the art, which is not considered to be of particular relevance

"B" state of the art documents or patents but published on or after the international filing date

"C" documents which may have priority claims or which are cited to establish the publication date of certain claims or other special reasons (see specification)

"D" documents referring to an oral disclosure, use, exhibition or other means

"E" documents published prior to the international filing date but later than the priority date claimed

"F" documents published after the international filing date or priority date and not in conflict with the applicant but cited to understand the principle or theory underlying the invention

"X" document of particular relevance the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance the claimed invention cannot be considered to involve an inventive step when the document is considered with one or more other such documents, such combinations being claimed in a patent claimed in the art

"Z" document member of the same patent family

Date of the actual completion of the international search

12 October 2001

Date of mailing of the international search report

19-10-2001

Name and mailing address of the ISA/

Swedish Patent Office

Box 5058, S-102 42 STOCKHOLM

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Authorized officer:

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Telephone No. +46 8 781 15 00

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/01240

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Character of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5929291 A (JERZY A. BAJGROWICZ ET AL), 27 July 1999 (27.07.99), scheme 1 and column 4, lines 52-55	1-3, 15-20
	--	
X	Organic Chemistry, Fifth Edition, T. W. Braham Solomons, John Wiley & Sons, Inc., New York, 1992, pages 781-782	8-9, 15-20
X	page 775	10, 15-20
X	pages 846-848; pages 830-832; pages 834-835	11-12, 15-20; 19, 15-20; 14-20
	--	
X	STN International, File CAPLUS, CAPLUS accession no. 1998:429075, Document no. 129:135904, Diaz-Requejo et al: "BpCu - Catalyzed Cyclopropanation of Olefins: A Simple System That Operates under and Heterogeneous Conditions (Bp = Dihydridobis(pyrazolyl)borate)"; & Organometallics (1998), 17(14), 3051-3057, RN 91993-54-3	21-22
	--	
X	STN International, File CAPLUS, CAPLUS accession no. 1998:250346, Document no. 128:321223, Galardon, Erwan et al: "Asymmetric cyclopropanation of alkenes and diazocarbonyl insertion into S-H bonds catalyzed by a chiral porphyrin Ru(II) complex"; & Tetrahedron Lett. (1998), 39(16), 2333-2334, RN 207270-36-5	21-22
	--	
X	STN International, File CAPLUS, CAPLUS accession no. 1995:927375, Document no. 124:116326, Dorocseau, A. et al: "Cyclopropanation catalyzed by RuCl3 (PPh3)3 and OsCl2(PPh3)3"; Tetrahedron Lett. (1995), 36(46), 8419-22, RN 4103-56-4, 4103-57-5	27-22

INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/01240

C (Classification). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1995:597880, Document no. 123:169063, Demonceau, A. et al: "Cyclopropanation of activated olefins catalyzed by Ru-phosphine complexes"; & Tetrahedron Lett. (1995), 36(20), 3519-22, RN 4103-56-4, 4103-57-5	21-22
X	STN International, File CAPLUS, CAPLUS accession no. 1998:200352, Document no. 128:270257, Kusuyama, Yoshiaki: "Solvolysis of 1-(trans-2-(m- or p-substituted phenyl) cyclopropyl)-1- methyl-ethyl p- nitrobenzoates"; & Bull. Chem. Soc. Jpn. (1998), 71(3), 685-691, RN 4103-57-5, 205674-79-9	21-22
X	Chemical Abstracts, Volume 59 (1962), (Columbus, Ohio, USA), Kaiser, Carl et al, "2-Substituted cyclopropylamines. I. Derivatives and analogs of 2-phenylcyclopropylamine", THE ABSTRACT No 504f, Med. Pharm. Chem. 1962, 5, 1243-1265, RN 91329-59-8, 91393-53-2, 92576-45-9	21-22
X	STN International, File CAPLUS, CAPLUS accession no. 2000:6701, Document no. 132:122310, Wu, Xin-Yan et al: "Asymmetric synthesis of 5-hydroxytryptamine receptor agonist (1R,2S)-(-)-2-(2-hydroxyphenyl)-N,N-dipropylcyclopropano"; & Gaocheng Xuexiao Huaxue Xuebao (1999), 20(12), 1892-1896, RN 256431-75-1, 256431-73-9	21-22
X	Chemical Abstracts, Volume 57 (1962), (Columbus, Ohio, USA), Richard Fuchs et al, "Transmission of electronic effects by the cyclopropane ring. Ionization constants of m- and p-substituted beta-phenylpropionic, cis- and trans-2-phenylcyclopropanecarboxylic acids in 50% ethanol", THE ABSTRACT No 33471, J. Org. Chem. 1962, 27, 733-736, RN 91329-60-1	21-22

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 01/01240

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of its relevant passages	Relevant to claim No.
X	STN International, File CAPLUS, CAPLUS accession no. 1996:148289, Document no. 124:250558, Vallgaard, Jørk et al: "trans-2-Aryl-N,N-dipropyl-cyclopropylamines: Synthesis and Interactions with 5-HT1A Receptors"; & J. Med. Chem. (1996), 39(7), 1485-93, RN 175168-73-7	21-22
X	WO 9905143 A1 (ASTRA PHARMACEUTICALS LTD.), 4 February 1999 (04.02.99)	21-22

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/SE 01/01240

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
US	5929291	A	27/07/99	EP	0801049 A	15/10/97
				EP	1008579 A	14/06/00
				JP	10036298 A	10/02/98
				US	6162954 A	19/12/00
				US	6236943 B	22/05/01
				US	6299314 B	29/05/01
				US	6284929 B	04/09/01
WO	9905143	A1	04/02/99	AU	8370698 A	16/02/99
				BR	9810802 A	12/09/00
				CN	1270590 T	18/10/00
				EE	200000044 A	16/10/00
				EP	0996621 A	03/05/00
				HU	0004333 A	28/04/01
				NO	20000312 A	21/03/00
				PL	338516 A	06/11/00
				SE	9702773 D	00/00/00
				SK	188199 A	09/10/00
				TR	200000197 T	00/00/00
				US	6251910 B	26/06/01
				SE	9702775 D	00/00/00
				ZA	9806050 A	06/04/99

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01240

Box I (Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet))

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Non:
because they relate to subject matter not required to be searched by this Authority; namely:
2. ☐ Claims Non:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Non:
because they are dependent claims and are not defined in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see next sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effect justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically by claims Non:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Non:

1-3, 8-14, 15-21 (partly)

Remark on Prior Art

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

Form PCT/IS0210 (second edition of first sheet (1)) (Only 1998)

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INTERNATIONAL SEARCH REPORT

PCT/SE01/01240

According to Article 34 (3) (a-c) and Rule 13.2, an international application shall relate to one invention only or to a group of inventions linked by one or more of the same or corresponding "special technical features", i.e. features, that define a contribution which each of the inventions makes over the prior art.

The problem the claimed invention aims to solve is to produce cyclopropyl carboxylic acid esters and other cyclopropyl carboxylic derivatives. This is performed in several steps where the essential step is the formation of a cyclopropyl compound from a α - β -unsaturated carbonyl compound by a reaction with dimethylsulfoxonium methylide (claim 1). Claims 2-3, which are associated with claim 1, describe the process step of claim 1 combined with the preparation of the reagent dimethylsulfoxonium methylide. Claims 4-7 relate to reaction steps leading the reactant of the process in claim 1 and these claims are formally connected to claim 1. Claims 8-14 relate to reactions of cyclopropyl compounds to produce cyclopropyl carboxylic derivatives. Each reaction step is described in independent claims.

The reaction described in claim 1 is however not new (March, J., Advanced organic chemistry: reactions, mechanisms and structure, 4th edition, 1992; Corey, E J, Chaykovsky, M, 1965). As this step is to be considered as the unifying special technical feature, there is no such feature, apart from the prior art, when this reaction is known. Consequently the present application does not fulfil the requirements of unity of invention.

The reactions, claimed in claims 4-14, are completely separated from the reaction described in claim 1. The division into several inventions is based on structural elements of the compounds. The characteristic element of the compound produced according to claim 1 is a substituted cyclopropyl. The reactions according to claims 4-7 do not involve compounds with this element. The reactions following the step in claim 1 do contain this characteristic structural element. However, as these reactions are described in independent claims not formally connected to a unifying step (the step of claim 1) each reaction step is considered to represent an independent invention. These inventions can however be searched for one fee.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE01/01240

The application also contains claims concerning the intermediate and end products of the process. In order to fulfil the requirements of unity of invention it is necessary that the intermediate compounds are closely interconnected with the end products. Such close connection requires that the essential structural part of the end product is incorporated by the intermediate. In the present invention the essential structural part is, as mentioned, a substituted cyclopropyl. This structural part is however not present in all the compounds claimed.

The application is found to contain the following inventions:

Inventions 1-7: Method for producing compound I and Ia and compounds exhibiting the same essential structural part (a substituted cyclopropyl) namely compounds V, Va, VI, VIa, VII, VIIa, VIII, VIIIa, IX and IXa. The compounds I, Ia, V, Va, VI, VIa, VII, VIIa, VIII, VIIIa, IX, IXa. This is described in claims 1-3, 5-14 and parts of claims 15-21.

Invention 8: Method for producing compound II and compound II. Claims 4-6 and part of claims 15-21.

Invention 9: Method for producing compound III and compound III and IV. Claim 7 and 15-16 partly.

As a consequence of the lack of unity of the application a complete search has not been performed. The search comprises only what is referred to as inventions 1-7 above.

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Applicant's or agent's file reference 100068-1 WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/ISA/416)	
International application No. PCT/SE01/01240	International filing date (day/month/year) 31.03.2001	Priority date (day/month/year) 02.06.2000
International Patent Classification (IPC) or national classification and IIC: C07C 67/347, C07C 69/003, C07C 69/017, C07C 69/743, C07C 69/753, C07C 61/04, C07C 69/96, C07C 233/56		
Applicant AstraZeneca AB et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims, and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 71.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Related statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 30.11.2001	Date of completion of this report 02.09.2002
Name and mailing address of the IP/EA/SE Patent- och registreringsverket Box 5008 S-102 42 STOCKHOLM Facsimile No. 05-657 72 88	Authorized officer Viveca Norén/35 Telephone No. 08-762 25 00

2. Basis of the report

1. With regard to the elements of the international application:**

- ☒ the international application as originally filed
- ☐ the description:
 pages _____, as originally filed
 pages _____, filed with the demand
 pages _____, filed with the letter of _____
- ☐ the claims:
 pages _____, as originally filed
 pages _____, as amended (together with any statement) under article 19
 pages _____, filed with the demand
 pages _____, filed with the letter of _____
- ☐ the drawings:
 pages _____, as originally filed
 pages _____, filed with the demand
 pages _____, filed with the letter of _____
- ☐ the sequence listing part of the description:
 pages _____, as originally filed
 pages _____, filed with the demand
 pages _____, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is.

- ☐ the language of a translation furnished for the purposes of international search (under Rule 33.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages _____
- ☐ the claims, Nos. _____
- ☐ the drawings, sheet/fig. _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2 (c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments shall be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.

PCT/SE01/01240

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 4-7, 15-22 partially

because:

- ☐ the said international application, or the said claims Nos. _____
relate to the following subject matter which does not require an international preliminary examination (specify):

- ☐ The description, claims or drawings (indicate particular elements below) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (specify):

- ☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

- ☒ no international search report has been established for said claims Nos. 4-7, 15-22 partially

2. A meaningful international preliminary examination cannot be carried out due to the failure of the applicant and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

- ☐ restricted the claims.
☐ paid additional fees.
☐ paid additional fees under protest.
☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirements of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirements of unity of invention in accordance with rules 13.1, 13.2 and 13.3 is

- ☐ complied with.
☒ not complied with for the following reasons:

According to Article 34 (3) (a-c) and Rule 13.2, an international application shall relate to one invention only or to a group of inventions linked by one or more of the same or corresponding "special technical features", i.e. features, that define a contribution which each of the inventions makes over the prior art.

The problem the claimed invention aims to solve is to produce cyclopropyl carboxylic acid esters and other cyclopropyl carboxylic derivatives. This is performed in several steps where the essential step is the formation of a cyclopropyl compound from a α - β -unsaturated carbonyl compound by a reaction with dimethylsulfoxonium methylide (claim 1). Claims 2-3, which are associated with claim 1, describe the process step of claim 1 combined with the preparation of the reagent dimethylsulfoxonium methylide. Claims 4-7 relate to reaction steps leading the reactant of the process in claim 1 and these claims are formally connected to claim 1. Claims 8-14 relate to reactions of cyclopropyl compounds to produce cyclopropyl carboxylic derivatives. Each reaction step is described in independent claims.

.../...

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

- ☐ all parts.
☒ the parts relating to claims Nos. 1-3, 8-14, 15-22 partially

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV

The reaction described in claim 1 is however considered as being obvious to a person skilled in the art (March, J, Advanced organic chemistry: reactions, mechanisms and structure, 4th edition, 1992; Corey, E J, Chaykovsky, M, 1965). This step is considered as the unifying special technical feature and as it is considered obvious to a person skilled in the art there is no such unifying feature apart from the prior art. Consequently the present application does not fulfil the requirements of unity of invention.

The reactions, claimed in claims 4-14, are completely separated from the reaction described in claim 1. The division into several inventions is based on structural elements of the compounds. The characteristic element of the compound produced according to claim 1 is a substituted cyclopropyl. The reactions according to claims 4-7 do not involve compounds with this element. The reactions following the step in claim 1 do contain this characteristic structural element. However, as these reactions are described in independent claims not formally connected to a unifying step (the step of claim 1) each reaction step is considered to represent an independent invention. These inventions have been included in the search and in this Preliminary Examination Report.

The application also contains claims concerning the intermediate and end products of the process. In order to fulfil the requirements of unity of invention it is necessary that the intermediate compounds are closely interconnected with the end products. Such close connection requires that the essential structural part of the end product is incorporated by the intermediate. In the present invention the essential structural part is, as mentioned, a substituted cyclopropyl. This structural part is however not present in all the compounds claimed.

The application is found to contain the following inventions:

Inventions 1-7: Method for producing compound I and Ia and compounds exhibiting the same essential structural part (a substituted cyclopropyl) namely compounds V, Va, VI, VIa, VII, VIIa, VIII, VIIIa, IX and IXa. The compounds I, Ia, V, Va, VI, VIa, VII, VIIa, VIII, VIIIa, IX, IXa. This is described in claims 1-3, 9-14 and parts of claims 15-22.

-/-

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of V

Invention 8: Method for producing compound II and compound II.
Claims 4-6 and part of claims 15-22.

Invention 9: Method for producing compound III and compound
III and IV. Claim 7 and 15-16 partly.

As a consequence of the lack of unity of the application a
complete search was not performed. The search comprised only
what is referred to as inventions 1-7 above. This Preliminary
Examination Report is based on the International Search Report
and relates likewise only to inventions 1-7.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; clarifications and explanations supporting such statement

1. Statement

Novelty (N)	Claims	<u>1-3, 6-20, 22</u>	YES
	Claims	<u>21</u>	NO
Inventive step (IS)	Claims		YES
	Claims	<u>1-3, 6-20, 22</u>	NO
Industrial applicability (IA)	Claims	<u>1-3, 8-22</u>	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

Reference is made to the following documents:

- 1) Journal of the American chemicals society, Volume 87, 1965, E. J. Corey et al: "Dimethylsulfonium Methylide ((CH₃)₂SOCH₂) and Dimethylsulfonium Methylide ((CH₃)₂SCH₂). Formation and Application to Organic Synthesis", page 1353 - page 1364
- 2) Advanced Organic Chemistry, Fourth Edition, Jerry March, "Reactions, Mechanisms, and structure, John Wiley & Sons, New York, 1992, pages 872, 741, pages 428-429, pages 1091-1095
- 3) US 5929291 A (JERZY A. BAGROWICZ ET AL; , 27 July 1999 (27.07.99), scheme 1 and column 4, lines 52-55
- 4) Organic Chemistry, Fifth Edition, T. W. Graham Solomons, John Wiley & Sons, Inc., New York, 1992, pages 781-782, page 775, pages 846-848; pages 830-832; pages 834-835
- 5) STN International, File CAPLUS, CAPLUS accession no. 1998:429075, Document no. 129:135904, Diaz-Requejo et al: "BpCu - Catalyzed Cyclopropanation of Olefins: A Simple System That Operates under and Heterogeneous Conditions (Bp = Dihydricobis(pyrazolyl)borate)"; & Organometallics (1998), 17(14), 3051-3057, RN 91393-54-3

-/-

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

- 7) STN International, File CAPLUS, CAPLUS accession no. 1998:250346, Document no. 128:321223, Galardon, Erwan et al: "Asymmetric cyclopropanation of alkenes and diazocarbonyl insertion into 5-H bonds catalyzed by a chiral porphyrin Ru(II) complex"; *J Tetrahedron Lett.* (1998), 39(16), 2333-2334, RN 207279-36-5
- 8) STN International, File CAPLUS, CAPLUS accession no. 1995:927375, Document no. 124:116326, Denonceanu, A. et al: "Cyclopropanation catalyzed by RuCl₃(PPh₃)₃ and OsCl₂(PPh₃)₃"; *Tetrahedron Lett.* (1995), 36(46), 8419-22, RN 4103-56-4, 4103-57-5
- 9) STN International, File CAPLUS, CAPLUS accession no. 1995:597980, Document no. 123:169063, Denonceanu, A. et al: "Cyclopropanation of activated olefins catalyzed by Ru-phosphine complexes"; *J Tetrahedron Lett.* (1995), 36(20), 3519-22, RN 4103-56-4, 4103-57-5
- 10) STN International, File CAPLUS, CAPLUS accession no. 1998:200362, Document no. 128:270257, Kusuyama, Yoshiaki: "Solvolysis of 1-(trans-2-(m- or p-substituted phenyl)cyclopropyl)-1-methyl-ethyl p-nitrobenzoates"; *J Bull. Chem. Soc. Jpn.* (1998), 71(3), 685-691, RN 4103-57-5, 205674-79-9
- 11) Chemical Abstracts, Volume 59 (1962), (Columbus, Ohio, USA), Kaiser, Carl et al: "2-Substituted cyclopropylamines. I. Derivatives and analogs of 2-phenylcyclopropylamine", THE ABSTRACT No 504f, *Med. Pharm. Chem.* 1962, 5, 1243 1265, RN 91329-59-8, 91393-53-2, 92576-45-9
- 12) STN International, File CAPLUS, CAPLUS accession no. 2000:6701, Document no. 132:122310, Wu, Xin-Yan et al: "Asymmetric synthesis of 5-hydroxytryptamine receptor agonist (1R,2S)-(-)-2-(2-hydroxyphenyl)-N,N-dipropylcyclopropamine"; *J Gaocheng Xuexiao Huaxue Xuebao* (1999), 20(12), 1692-1696, RN 256431-75-1, 256431-73-9

.../...

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

13) Chemical Abstracts, Volume 57 (1962), (Columbus, Ohio, USA), Richard Fuchs et al: "Transmission of electronic effects by the cyclopropane ring. Ionization constants of m- and p-substituted. beta.-phenylpropionic, cis- and trans-2-phenylcyclopropanecarboxylic acids in 50% ethanol", THE ABSTRACT No 33471, J. Org. Chem. 1962, 27, 733-736, RN 91329-60-1

14) STN International, File CAPLUS, CAPLUS accession no. 1996:148289, Document no. 124:250558, Valigaarda, Jerk et al: "trans-2-Aryl-N,N-dipropyl-cyclopropylamines: Synthesis and Interactions with 5-HT1A Receptors"; J. Med. Chem. (1996), 39(7), 1485-93, RN 175168-73-7

15) WO 9905143 A1 (ASTRA PHARMACEUTICALS LTD.), 4 February 1999 (04.02.99)

Document D1 discusses the preparation and reactions of dimethyloxosulfonium methylide (another name for dimethylsulfoxonium methylide) and dimethylsulfonium methylide. One of the reactions discussed is the formation of cyclopropyl ketones from α,β -unsaturated ketones with dimethyloxosulfonium methylide.

D2 (page 872) shows a general reaction where dimethyloxosulfonium methylide converts double-bond compounds to cyclopropane derivatives. D3 discloses novel compounds and processes to obtain these compounds. One of the reaction steps is the cyclopropanation of α,β -enones using dimethyloxosulfonium methylide or other ylides.

According to D1-D3 reactions where a methylene group is added to the C-C double bond in α,β -unsaturated carbonyls are previously known. These reactions are the same type of reaction as is described in claim 1 of the present application although they are performed with other compounds. It is however considered obvious to a person skilled in the art to try to apply this type of reaction also on other similar substances. The invention is therefore considered to lack inventive step.

.../...

Supplemental Box

(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: V

From D1 it is also known to prepare dimethyloxosulfonium methylide by reacting trimethyloxosulfonium chloride or iodide with sodium hydride. To try to perform this reaction with a weaker base than a hydride, e.g. a metal hydroxide as in step i) in claim 2 of the present application, seems to be an possibility to a person skilled in the art. Step ii) is according to the discussion above also considered to be obvious to a person skilled in the art and the invention according to claims 2-3 is considered to lack inventive step.

The reactions claimed in claims 8-14 are all standard procedures which are described in documents D2 and D4 and what is described in claims 15-20 are only embodiments of the invention which are obvious to someone skilled in the art. The invention according to claims 8-20 is not considered to involve an inventive step.

Documents D5-D14 disclose compounds comprised by the general formulas of claim 21 and which are similar to the compounds in claim 22. The invention according to claim 21 is therefore not novel and the invention according to claim 22 is considered to lack inventive step.

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference

(if desired) (12 characters maximum) 100068-1 WO

Box No. I TITLE OF INVENTION
NOVEL PROCESS

Box No. II APPLICANT

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.)

AstraZeneca AB
S-151 85 Södertälje
Sweden

☐ This person is also inventor.

Telephone No.

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Facsimile No.

+46 8 553 288 20

Teleprinter No.

State (that is, country) of nationality:

SE

State (that is, country) of residence:

SE

This person is applicant for the purposes of:

☐ all designated States

☒ all designated States except the United States of America

☐ the United States of America only

☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AN INVENTOR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.)

CLARK, Adrian
AstraZeneca R&D Södertälje
S-151 85 Södertälje
Sweden

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (if this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

AU

State (that is, country) of residence:

SE

This person is applicant for the purposes of:

☐ all designated States

☐ all designated States except the United States of America

☒ the United States of America only

☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

Global Intellectual Property
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☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

54

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

JONES, Eilyn
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Sweden

This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only (if this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
GB

State (that is, country) of residence:
SE

This person is applicant for the purposes of:

- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Part

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

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This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only (if this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
SE

State (that is, country) of residence:
SE

This person is applicant for the purposes of:

- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Part

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

MINIÖIS, Anna
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Sweden

This person is:

- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only (if this check-box is marked, do not fill in below.)

State (that is, country) of nationality:
SE

State (that is, country) of residence:
SE

This person is applicant for the purposes of:

- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Part

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

This person is:

- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only (if this check-box is marked, do not fill in below.)

State (that is, country) of nationality:

State (that is, country) of residence:

This person is applicant for the purposes of:

- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Part

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) (mark the applicable check-boxes; at least one must be marked):

Regional Patent

- ☐ AP ARIPO Patent: GT Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SI Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☐ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☐ EP European Patent: AT Austria, BE Belgium, CH and LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☐ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line)

- | | |
|---|---|
| ☐ AE United Arab Emirates | ☐ LC Saint Lucia |
| ☐ AG Antigua and Barbuda | ☐ LK Sri Lanka |
| ☐ AL Albania | ☐ LR Liberia |
| ☐ AM Armenia | ☐ LS Lesotho |
| ☐ AT Austria | ☐ LT Lithuania |
| ☐ AU Australia | ☐ LU Luxembourg |
| ☐ AZ Azerbaijan | ☐ LV Latvia |
| ☐ BA Bosnia and Herzegovina | ☐ MA Morocco |
| ☐ BB Barbados | ☐ MD Republic of Moldova |
| ☐ BG Bulgaria | ☐ MG Madagascar |
| ☐ BR Brazil | ☐ MK The former Yugoslav Republic of Macedonia |
| ☐ BY Belarus | ☐ MN Mongolia |
| ☐ BZ Belize | ☐ MW Malawi |
| ☐ CA Canada | ☐ MX Mexico |
| ☐ CH and LI Switzerland and Liechtenstein | ☐ MZ Mozambique |
| ☐ CN China | ☐ NO Norway |
| ☐ CR Costa Rica | ☐ NZ New Zealand |
| ☐ CU Cuba | ☐ PL Poland |
| ☐ CZ Czech Republic | ☐ PT Portugal |
| ☐ DE Germany | ☐ RO Romania |
| ☐ DK Denmark | ☐ RU Russian Federation |
| ☐ DM Dominica | ☐ SD Sudan |
| ☐ DZ Algeria | ☐ SE Sweden |
| ☐ EE Estonia | ☐ SG Singapore |
| ☐ ES Spain | ☐ SI Slovenia |
| ☐ FI Finland | ☐ SK Slovakia |
| ☐ GB United Kingdom | ☐ SL Sierra Leone |
| ☐ GD Grenada | ☐ TJ Tajikistan |
| ☐ GE Georgia | ☐ TM Turkmenistan |
| ☐ GH Ghana | ☐ TR Turkey |
| ☐ GM Gambia | ☐ TT Trinidad and Tobago |
| ☐ GR Greece | ☐ TZ United Republic of Tanzania |
| ☐ GT Guatemala | ☐ UA Ukraine |
| ☐ GU Guam | ☐ UG Uganda |
| ☐ HK Hong Kong | ☐ US United States of America |
| ☐ HN Hungary | ☐ UZ Uzbekistan |
| ☐ ID Indonesia | ☐ VN Viet Nam |
| ☐ IL Israel | ☐ YU Yugoslavia |
| ☐ IN India | ☐ ZA South Africa |
| ☐ IS Iceland | ☐ ZW Zimbabwe |
| ☐ JP Japan | |
| ☐ KE Kenya | |
| ☐ KG Kyrgyzstan | |
| ☐ KP Democratic People's Republic of Korea | |
| ☐ KR Republic of Korea | |
| ☐ KZ Kazakhstan | |

Check-box reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☐ CO Colombia ☐ EC Ecuador

Preventive Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 13 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

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Box No. VI PRIORITY CLAIM		☐ Further priority claims are indicated in the Supplemental List.		
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application: regional Office	international application: receiving Office
Item (1) 02.06.2000 (02 June 2000)	0013487.4	Great Britain (GB)		
Item (2) 06.06.2000 (06 June 2000)	0002101-4	Sweden (SE)		
Item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office) identified above as item(s): (2)

* Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental List at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.1(c)(4)). See Supplemental List.

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / SE

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year)

29 Nov 2000

Number

SE00/00652

Country (to regional Office)

Sweden

Box No. VIII CHECK LIST: LANGUAGE OF FILING

This international application contains the following number of sheets:

request : 4

description (excluding sequence listing part) : 13

claims : 6

abstract : 1

drawings :

sequence listing part of description :

Total number of sheets : 23

This international application is accompanied by the item(s) checked below:

1. ☒ fee calculation sheet
2. ☒ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any: GFAS/2001
4. ☐ statement explaining lack of signature
5. ☒ priority document(s) identified in Box No. VI as item(s): (1)
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☒ other (specify): ITS Report SE00/00652

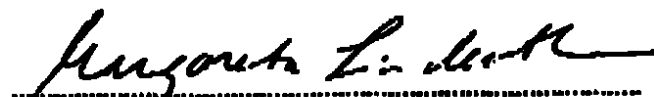
Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request)

Södertälje, 31 May 2001



Margareta Linderöth
Global Intellectual Property, AstraZeneca AB

For receiving Office use only		2. Drawings: ☐ received; ☐ not received;
1. Date of actual receipt of the purported international application:		
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required correction under PCT Article 1(2):		
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid.	

For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more authorities are competent, with the one chosen by the applicant. The full name or two-letter code of this authority may be indicated by the applicant on the line below.

IPEA/ SE

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty.

The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IP EA	Date of receipt of DEMAND
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION Applicant's or agent's file reference 100068-1 WO	
International application No. PCT/SE01/01240	International filing date (day/month/year) 31 May 2001 (31.05.2001) (Earliest) Priority date (day/month/year) 2 June 2000 (02.06.2000)
Title of invention NOVEL PROCESS	
Box No. II APPLICANT(S)	
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.) AstraZeneca AB S-151 85 Södertälje Sweden	Telephone No. +46 8 553 280 00 Facsimile No. +46 8 553 288 20 Teleprinter No. Applicant's registration No. with the Office
State (that is, country) of nationality: SE	State (that is, country) of residence: SE
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.) CLARK, Adrian AstraZeneca R&D Södertälje S-151 85 Södertälje Sweden	
State (that is, country) of nationality: AU	State (that is, country) of residence: SE
Name and address: (Family name followed by given names; for a legal entity, full official designation. The address must include postal code and name of country.) JONES, Eilyn AstraZeneca R&D Södertälje S-151 85 Södertälje Sweden	
State (that is, country) of nationality: GB	State (that is, country) of residence: SE
☒ Further applicants are indicated on a continuation sheet.	

Continuation of Box No. II APPLICANT(S)

If none of the following sub-items is used, this sheet should not be included in the demand.

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

LARSSON, Ulf
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S-151 85 Södertälje
Sweden

State (that is, country) of nationality:

SE

State (that is, country) of residence:

SE

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

MINIDIS, Anna
AstraZeneca R&D Södertälje
S-151 85 Södertälje
Sweden

State (that is, country) of nationality:

SE

State (that is, country) of residence:

SE

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

State (that is, country) of nationality:

State (that is, country) of residence:



Further applicants are indicated on another continuation sheet.

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representativeand ☒ has been appointed earlier and represents the applicant(s) also for international preliminary examination.☐ is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.☐ is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.Name and address: (Family name followed by given name; for a legal entity, full official designation.
The address must include postal code and name of country.)Global Intellectual Property, Patents
AstraZeneca AB
S-151 85 Söderlälje
Sweden

Telephone No.

+46 8 553 260 00

Facsimile No.

+46 8 553 268 20

Teleprinter No.

Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV. BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:

1. The applicant wishes the international preliminary examination to start on the basis of:

☒ the international application as originally filedthe description ☐ as originally filed
☐ as amended under Article 34the claims ☐ as originally filed
☐ as amended under Article 19 (injection with any accompanying amendment)
☐ as amended under Article 34the drawings ☐ as originally filed
☐ as amended under Article 342. ☐ The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.3. ☐ The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). (This check-box may be marked only where the time limit under Article 19 has not yet expired.)

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: English☒ which is the language in which the international application was filed.☐ which is the language of a translation furnished for the purposes of international search.☐ which is the language of publication of the international application.☐ which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States (that is, all States which have been designated and which are bound by Chapter II of the PCT)

excluding the following States which the applicant wishes not to elect:

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:

- | | | |
|--|---|--------|
| 1. translation of international application | : | sheets |
| 2. amendments under Article 34 | : | sheets |
| 3. copy (or, where required, translation) of amendments under Article 19 | : | sheets |
| 4. copy (or, where required, translation) of statement under Article 19 | : | sheets |
| 5. letter | : | sheets |
| 6. other (specify) | : | sheets |

For International Preliminary Examining Authority use only
received not received

- | | |
|--------------------------|--------------------------|
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |
| ☐ | ☐ |

The demand is also accompanied by the item(s) marked below:

- | | |
|--|--|
| 1. ☒ fee calculation sheet | 5. ☐ statement explaining lack of signature |
| 2. ☐ original separate power of attorney | 6. ☐ sequence listing in computer readable form |
| 3. ☐ original general power of attorney | 7. ☐ other (specify): |
| 4. ☒ copy of general power of attorney, reference number, if any: GF 3502/2001 | |

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

Södenälje, 30 November 2001



Christer Wahlström
Global Intellectual Property, Patents, AstraZeneca AB

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:

2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):

- | | |
|--|---|
| 3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. | ☐ The applicant has been informed accordingly. |
| 4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 60.5. | |
| 5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 62. | |

For International Bureau use only

Demand received from IPEA on:



CONSULADO GENERAL DE COLOMBIA

3RD FLOOR, 15-19 RIFAT TITCHFIELD STREET, LONDON W1P 7PB
TELEPHONE 020-7837 8803 • TELEFAX 020-7837 5804
E MAIL consulco@consulco.london.mil

El suscrito Cónsul General de Colombia en Londres, vistos los documentos presentados ante este Despacho,

CERTIFICA

Que, J.B. HODGSON, Notario Público de Macclesfield, Cheshire, Inglaterra, legalizó la firma del documento precedente y su firma se encuentra certificada por J. GARRIHAN, Oficial de del Ministerio de Relaciones Exteriores Británico, firma que se encuentra registrada en este Consulado General.

Que, AstraZeneca AB, es una Sociedad constituida, organizada y existente en Suecia, y que cumple con su objeto social de acuerdo con las leyes de ese país.

Que, DAVID ERIC GILES, en su calidad de Representante Legal de la mencionada Sociedad, debidamente autorizado otorga el documento precedente y su firma se encuentra legalizada por J.B. HODGSON, Notario Público de Macclesfield, Cheshire, Inglaterra, Gran Bretaña.

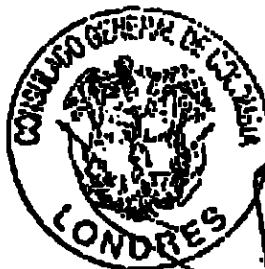
El Cónsul General no asume responsabilidad por el contenido del mencionado documento.

Dado en Londres, Inglaterra, Gran Bretaña, a los quince (15) días del mes de Noviembre de dos mil (2000).

Certificación No.11 /1722

Derechos: LIS 106,00 CANCELADOS


CLAUDIO H. BERRIO VILLARREAL
Cónsul General



HUGO NAVARRO ALVARADO
TRADUCTOR E INTERPRETE OFICIAL
Bta 1872 (Londres) 1990



BRIGARD & CASTRO

SANTAFE DE BOGOTA - COLOMBIA

PODER

Yo (nuestros) ASTRAZENECA AB

Domiciliado(s) en: S-151 85, Soderlajla,
SUECIA

Nombre(amos) a. RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, de Santafé de Bogotá, Colombia, apoderados verdaderos y legales con poder especial, amplio y suficiente, para recabar de las oficinas y autoridades colombianas administrativas, judiciales y de policía, en cualquier instancia o recurso, la obtención de patentes de invención, registros de marcas, diseños industriales, modelos de utilidad, depósitos de nombres comerciales y emblemas, registros de derechos de autor y contratos sobre los mismos, obtención de certificaciones de obtentor de variedades vegetales, así como sus prórrogas, renovaciones, anotaciones de traspaso, cambios de nombre y/o domicilio; elaborar, tramitar y registrar contratos de licencia y licencias de cualesquiera cosas, intervenir como demandante o como demandado en cualquier instancia y recurso ante cualquier juez, corporación, funcionario público o autoridad en acciones judiciales, administrativas y de policía tales como: oposiciones al registro de marcas; acciones de caducidad, cancelación y nulidad; acciones reivindicatorias, acciones derivadas de la obtención u explotación de licencias; acciones de competencia desleal; demandas penales; acciones de indemnización de perjuicios, reclamos y observaciones a solicitudes de patentes, diseños industriales, modelos de utilidad, en el ejercicio de medidas cautelares y en otras acciones o medidas similares.

A este efecto, lo(s) faculto(amos) para elevar solicitudes, formular descripciones, enmiendas, protestas, declaraciones, oposiciones, cancelaciones, nulidades, apelaciones y reclamos; pagar impuestos, cuotas y gravámenes prescritos por la ley, renunciar o desistirse a derechos concedidos o en curso de concesión; recibir toda clase de documentos y valores, dando el descargo respectivo, y, en general, para dar ante dichas autoridades todas las pasos necesarios al efecto indicado y tomar todas las medidas que creyeran conducentes al resguardo de mis (nuestros) intereses), con todas las demás facultades legales necesarias.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo efectuado así como la facultad de desistir, transigir, comprometer y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: RAMIRO CASTRO DUQUE y/o HECTOR GOMEZ MEJIA, domiciliado(s) en la Carrera 7 No. 16-56 Piso 8, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

Elaborado y firmado en

hoy de de 20

Firma

Nombre
Cargo

POWER OF ATTORNEY

I (We) ASTRAZENECA AB

Domiciled in: S-151 85, Soderlajla
SWEDEN

Hereby appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA, of Santafé de Bogotá, Colombia, my (our) true and lawful attorneys with special, ample and sufficient power to obtain from the Colombian administrative, judicial and police offices and authorities, in any instance, privileges of patents of invention, registration of trademarks, industrial designs and utility models; registration of commercial names and emblems, registration of copyright and contracts related thereto, certificates of obtainment of vegetable varieties, as well as extensions, renewals and recordal of assignments and changes of name and domicile related to the above; to prepare, prosecute and register licenses of any kind; to act as plaintiff or defendant in any instance or recourse, and before any judge, corporation, public official or authority in judicial, administrative and police actions, such as: oppositions to the registration of trademarks, caducity, cancellation and nullity actions; claim actions derived from the obtaining or exploitation of licenses, action of unfair competition; penal demands, actions of indemnities for damages; claims or observations on patent applications, models, industrial designs and utility models; in the exercise of preventive measures; and in other actions or similar proceedings.

To that effect they hereby empowered to file applications, formulate descriptions, amendments, protests, declarations, oppositions, cancellations, nullities, appeals and claims; to pay taxes, quotas and assessments prescribed by law, renounce or waive the rights granted or in the process of granting; to receive all kinds of documents and valuables, giving the respective release of receipt, and, in general, to take before said authorities the necessary steps to such effect, and any measures that they may deem pertinent to the safeguard of my (our) interests) with all the other necessary legal powers.

This power includes the faculty to ratify or confirm, desist, settle and compromise on my (our) behalf, and to substitute this power in whole or in part and to revoke substitutions. I (We) hereby appoint RAMIRO CASTRO DUQUE and/or HECTOR GOMEZ MEJIA, domiciliado(s) en la Carrera 7 No. 16-56, Piso 8, my (our) attorneys in Colombia, with powers to receive notifications and to designate judicial and extrajudicial attorneys.

Granted and signed in

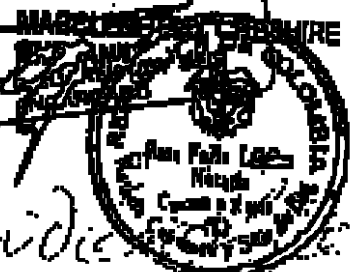
This 10 May 2004

Signature

Name
Title

DAVID ERIC GILES
DIRECTOR IP SERVICES

DAVID ERIC GILES
DIRECTOR IP SERVICES



CERTIFICAD NOTARIAL (SOCIEDAD)

Hoy de de
Personalmente compareció ante mí

a quien conozco, y de quien me consta que firmó el
anterior documento, debidamente juramentado declaró y
dijo que él es

De ASTRAZENECA AB

Sociedad legalmente constituida para un periodo de
duración que aún no ha terminado; que el declarante
está autorizado por dicha compañía para conferir este
poder; que el sello estampado por él al p/a de tal poder,
en nombre y representación de la expresada compañía,
es el sello oficial de ella; y que el objeto para el cual se
confiere este instrumento está comprendido dentro del
de la sociedad.

El suscrito Notario hace constar que tuvo a la vista las
pruebas de la existencia de la sociedad

Estado de
con fecha

y que quien confiere el presente poder es su
representante.

Notario Público (sello)

**CERTIFICADO NOTARIAL
PERSONA NATURAL**

Hoy de de
compareció(eron) ante mí

a quien (es) conozco y me consta que se(son) la(s)
persona(s) firmante(s) del documento que precede y
quien(es) declara(n) que otorgan el presente poder para los
y propósitos que en él se expresan.

Notario Público (sello)

NOTARIAL CERTIFICATE (CORPORATION)

On this 10 day of November of 2000
Personally appeared before me

DAVID ERIC GILES
to me known, and known to me to be the person who
signed the foregoing instrument who being by me duly
sworn did depose and say that he (she) is the

DIRECTOR IP SERVICES

of ASTRAZENECA AB

Which is legally constituted for a term not yet expired,
that deponent is authorized by said Company to confer
this Power of Attorney; that the seal affixed hereunto by
the deponent in the name and on behalf of said
Corporation is the corporate seal thereof; and that the
purpose for which this instrument is granted is included
within the corporate purpose of company.

The undersigned Notary Public attests that he has seen
the documents that prove the existence of the company.

State of Sweden
under date of 30 JANUARY 2000

and that he (she) who grants the present power of
attorney is its Representative.

Notary Public (Seal)

**NOTARIAL CERTIFICATE
NATURAL PERSON**

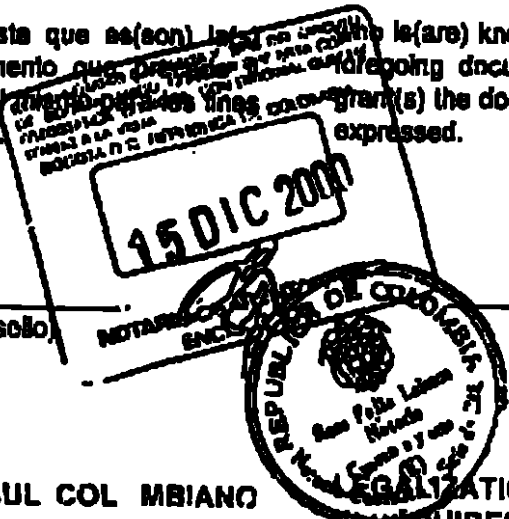
On this day of of
personally appeared before me

who le(are) known to me and who I attest executed the
foregoing document and he (they) declared he (they)
grant(s) the document for the uses and purposes therein
expressed.

Notary Public (Seal)

LEGALIZACION ANTE CONSUL COL MBIANO
ES REQUERIDA

LEGALIZATION BEFORE COLOMBIAN CONSUL
IS REQUIRED



63

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

No. D644894

Date 14 November, 2000

This document bears
the signature / seal of J. H. Hodgson

1954 - 1955 ALVAREZ
1956 - 1957 INTERPRETE OTICIAL
1958 - 1959 ALVAREZ

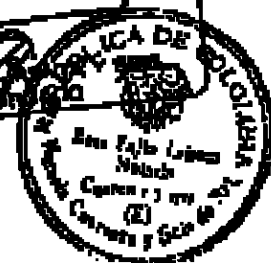
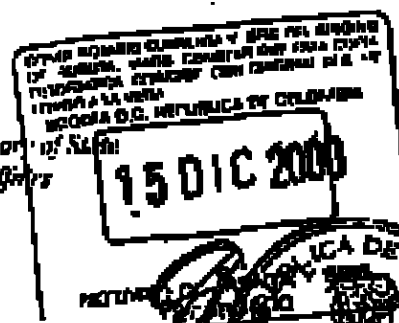
Acting in the capacity of Notary Public

Signed by: J. Garbarran



[Handwritten signature]

For Her Majesty's Principal Secretary of State
For Foreign and Commonwealth Affairs



64

TRADUCCION OFICIAL No. 432/2000 de las legalizaciones que se encuentran a continuación de un Poder otorgado ASTRAZENECA AB, una compañía domiciliada en S-151 85, Gaderlaga, SUECIA al doctor RAMIRO CASTRO y HÉCTOR GOMEZ, Santafé de Bogotá, D.C., Colombia, del Inglés al español, las cuales para su identificación se sella con el Bello del Traductor al mismo tiempo que la presente.-

ANEXOS: El Poder arriba mencionado, Certificación Notarial, Certificación por el Secretario de Estado Principal de Su Majestad Para los Asuntos de la Comunidad y el Extranjero en Londres, Inglaterra, Certificación del Consulado General de Colombia en Londres, Inglaterra, Autenticación por el Ministerio de Relaciones Exteriores de Colombia.-

**Firma ilegible (Firmado)
Notario Público
BELLO NOTARIAL EN RELIEVE.**

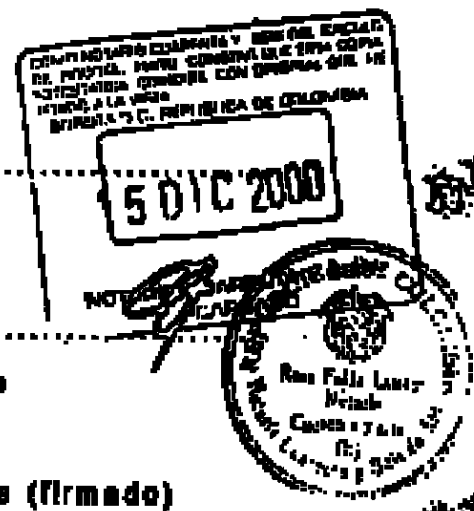
REINO UNIDO DE LA GRAN BRETAÑA E IRLANDA DEL NORTE

**No. D644894
Fecha...14 de Noviembre del año 2000.....
Este documento porta
la firma/sello de J. B. Hodgeson
.....
actuando en la capacidad de
Notario Público**

Firmado por: J. Garbrah

Firma ilegible (Firmado)

**HUBO NAVARRO ALVAREZ
TRADUCCION E INTERPRETE OFICIAL
P.O. BOX 141400, MIAMI, FL 33114**



86
65

Por el Secretario de Estado Principal de
Su Majestad para los Asuntos de la
Comunidad y el Extranjero.

SELLO EN RELIEVE.

HAY SELLO DE LA COMUNIDAD
Y EL EXTRANJERO EN LONDRES,
INGLATERRA.

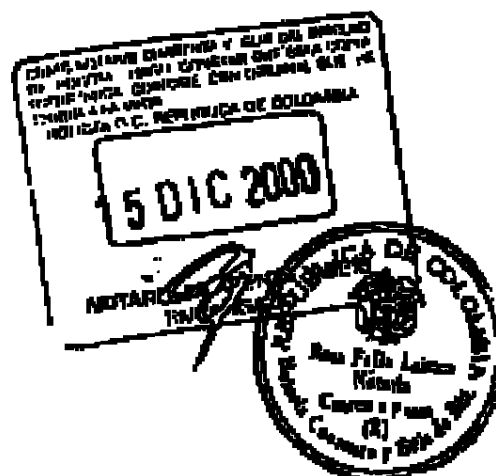
+++++
EN ESPAÑOL: La Certificación del Consulado General de Colombia
en Londres, Inglaterra bajo el Número de Certificación 11/1722 de
fecha 16 de Noviembre del año 2000; Autenticación Hasia por el
Ministerio de Relaciones Exteriores de Colombia bajo el Número
481834 de fecha 29 de Noviembre del año 2000.

(Pagados Derechos por valor de \$100.00 Dólares)

+++++
ES TRADUCCION FIEL Y COMPLETA DE LOS DOCUMENTOS
ADJUNTOS.

Hugo Navarro Alvarez
HUGO NAVARRO ALVAREZ
TRADUCCION E. INTERPRETE OFICIAL
Dir. 1876 No. 2000-100

Resolución Número 1876 del Ministerio de Justicia
Fecha: 4 de Diciembre del año 2000.





OFFICE OF THE
MAYOR
GUAYAMA, P.R.

Mayor

GUAYAMA, P.R.

GUAYAMA, P.R.

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
MODELO DE UTILIDAD	()	()
- Indicación de que se solicita la concesión de una patente.	()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
- Descripción de la invención.	()	()
- Dibujos de ser estos pertinentes.	()	()
- Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()
DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()	INCOMPLETA ()	()
ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA ()	INCOMPLETA ()	()

Firma Responsable:

Fecha:

68
67



Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctor:
Ramiro Castro Duque
Apoderado
ASTRAZENECA AB

Oficio N° 06846

ASUNTO:	Radicación N°	02-109618
	Solicitud internacional	PCT/SE01/01240
	Fecha inicio fase nacional	02/01/2003
	Tránsito	011
	Evento	379
	Actuación	430
	Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 25-k Decisión 486).
- La solicitud no contiene la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT).

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

AUX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha 22 ABO. 2003