

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



DELEGATURA PROPIEDAD INDUSTRIAL

División de Nuevas Creaciones

SOLICITUD

PATENTE DE INVENCION

ENTRADA EN FASE NACIONAL

04-129311

21. EXPEDIENTE No.

54. TITULO PROCESO PARA LA PREPARACION DE ESTERES DE ACIDO DIOXAN ACETICO

51. CLASIFICACION INTERNACIONAL A61K31/22

71. SOLICITANTE ASTRAZENECA UK LIMITED

DOMICILIO LONDON W1K 1LN, INGLATERRA

74. APODERADO JUAN PABLO CADENA SARMIENTO

22. SANTAFE DE BOGOTA, D.C. 28/12/2004

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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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
(71)Nombre: **ASTRAZENECA UK LIMITED**Dirección: 15 Stanhope Gate, London W1K 1LN
InglaterraNacionalidad o Domicilio: Inglaterra
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E-mail

IDENTIFICACION

C.C. ☐ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número _____

3

REPRESENTANTE
O APODERADONombre: **JUAN PABLO CADENA SARMIENTO**

Dirección: Cra. 7 No. 16-56 Piso 9

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IDENTIFICACION

C.C. ☒ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número 80.410.337 TP_57492

4

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Houthalen, BE; Gaspeldoornstraat 32, NL-5925 BA Venlo, NL; Geleentraat 70, NL-6155
ND Puth, Holanda (Respectivamente)
Nacionalidad o Domicilio: Holanda y Bélgica (Respectivamente)

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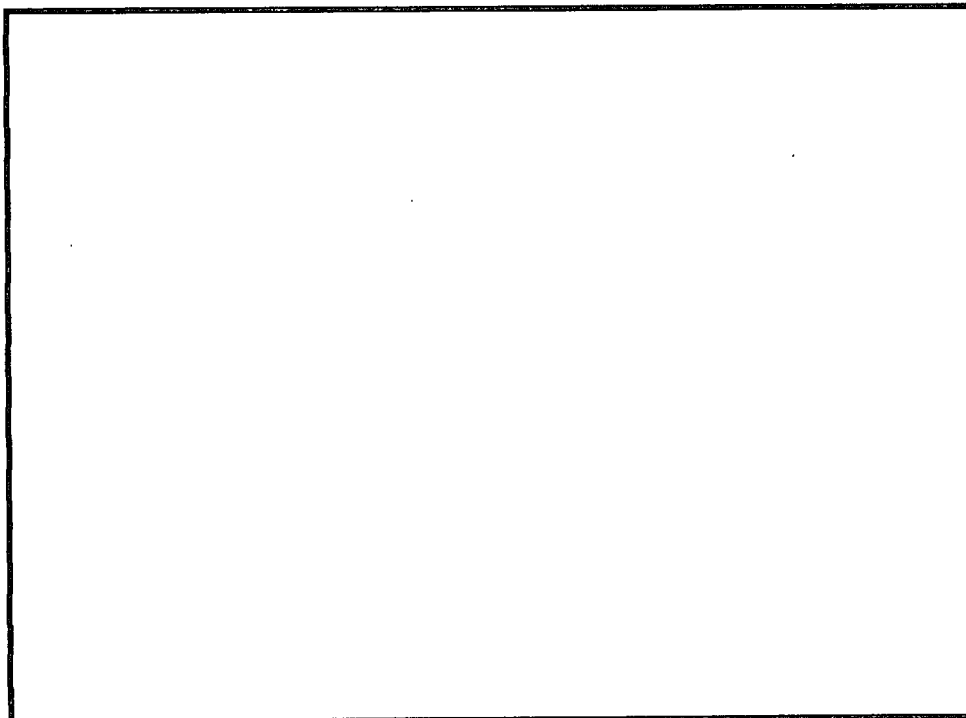
Instrucciones para el diligenciamiento del presente formulario, ver reverso de esta página.

10

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud. \$422.000
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso. **Fotocopia Autenticada**
- ☐ 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.
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- ☐ 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 Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:



12 Solicito la concesión de la patente,

NOMBRE: JUAN PABLO CADENA SARMIENTO

FIRMA:

Juan Pablo Cadena
C.C. 80.410.337 de Usaquén T.P. 57492 del C.S.J.

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

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Radicación: 84129311 80003008 Folios: 51
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Dependencia: 8000 DIVISION DE NUEVAS CREACIONES

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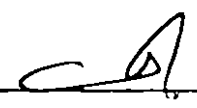
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	28028759	01/12/2004	23,220,000.00

***** CONCEPTO *****

CANT. CONTABILISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	422,000.00
	TOTAL :	\$ 422,000.00

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

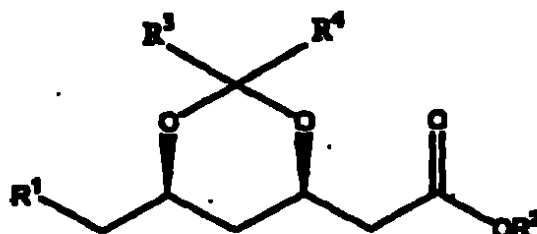
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SI, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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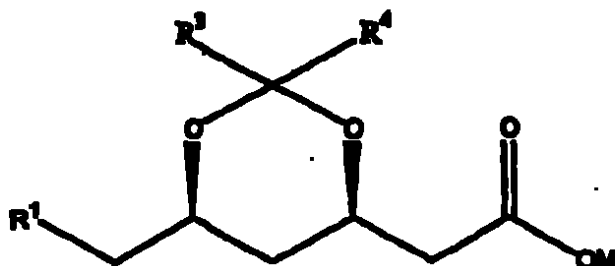
— with international search report

[Continued on next page]

(34) Title: PROCESS FOR THE PREPARATION OF DIOXANE ACETIC ACID ESTERS



(1)



(2)

(57) Abstract: Process for the preparation of an ester of formula (1), wherein R¹ represents a leaving group, CN, OH or a COOR³ group, R³ and R⁴ each independently represent a 1-3 C alkyl group, and R² and R⁵ each independently represent an ester residue, wherein the corresponding salt with formula (2), wherein M represents H or an alkali (earth) metal in an inert solvent is contacted with an acid chloride forming agent to form the corresponding acid chloride, and the acid chloride is contacted with an alcohol with formula R²OH in the presence of N-methyl-morpholine. Preferably M represents an alkali metal, and R² represents an alkyl group, particularly a t-butyl group. (1), (2)

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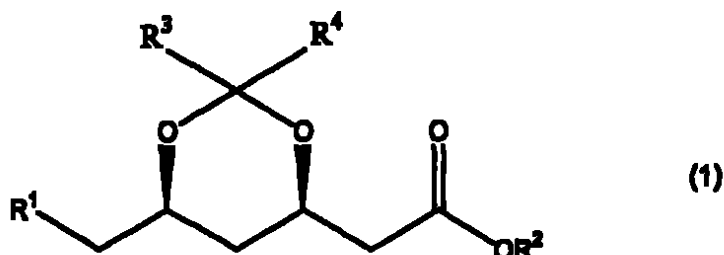
WO 03/106447 A1



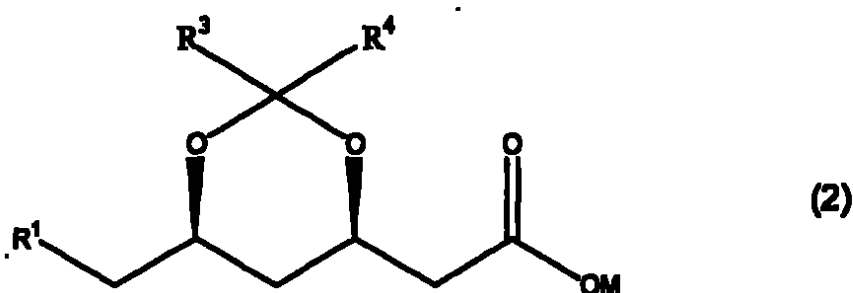
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PROCESS FOR THE PREPARATION OF DIOXANE ACETIC ACID ESTERS

- 5 The invention relates to a process for the preparation of an ester of formula (1)



- 10 wherein R¹ represents a leaving group, CN, OH or a COOR⁵ group, R³ and R⁴ each independently represent a C1-3 alkyl group and R² and R⁵ each independently represent an ester residue, wherein the corresponding salt with formula (2)



- 15 wherein M represents H or an alkali (earth) metal in an inert solvent is contacted with an acid chloride forming agent to form the corresponding acid chloride, and the acid chloride is contacted with an alcohol with formula R²OH in the presence of N-methyl morpholine (NMM).

- 20 Many processes for the preparation of esters are known in the art, for instance the preparation of esters via the formation of the acid chloride. It was, however, to be expected that such processes would not lead to high yields due to the lack of stability of the present compound under acidic conditions.

It is the object of the invention to provide a process for the

preparation of esters with high yield in a robust process, even at large scale and with relatively high concentrations.

Surprisingly it has been found that even sterically hindered esters that are difficult to obtain in esterifications like t-butyl esters of the acid unstable molecules of formula (1), can be obtained in high yield in an easily reproducible process.

With the process according to the invention esters with formula (1) that are unstable under acidic conditions, for instance with $\text{pH} < 4$, can be prepared in high yield.

R^1 represents a leaving group, CN, OH or a COOR^5 group wherein R^5 represents an ester residue, for example an alkyl group with for instance 1-6 C-atoms, or an aryl group with for instance 6-12 C-atoms. A leaving group by definition is a group that can easily be replaced, for example a halogen, for instance Cl, Br or I; a tosylate group; a mesylate group; an acyloxy group, with, for instance, 1-6 C-atoms in particular an acetoxy group; a phenacetyloxy group; an alkoxy group with, for instance, 1-6 C-atoms or an (hetero) aryloxy group with, for instance, 6-12 C-atoms. Preferably R^1 represents Cl.

R^2 represents an ester residue, preferably an alkyl group, for instance an alkyl group with 1-6 C-atoms or an aryl group, for instance an aryl group with 6-12 C-atoms, in particular a methyl, ethyl, propyl, isobutyl or t-butyl group. An important group of esters that can be prepared with the process according to the invention are t-butyl esters.

R^3 and R^4 each independently represent a C1-C3 alkyl group, for instance a methyl or ethyl group. Preferably R^3 and R^4 both represent methyl.

M in formula (2) can be chosen from the group of H, alkali metals, for instance lithium, sodium, potassium and alkali earth metals, for instance magnesium or calcium. Preferably M represents sodium or potassium.

The acid chloride forming agent can be chosen from the group of reagents that is generally known as such. Suitable examples of acid chloride forming agents are oxalyl chloride, thionyl chloride, PCl_5 , PCl_3 , and POCl_3 . Preferably the acid chloride forming agent is used in an excess relative to the amount the salt with formula (2), for instance between 1 and 3 equivalents, more preferably between 1.2 and 1.8 equivalents.

If desired, in the acid chloride formation also a catalyst may be present. The amount of catalyst may for instance vary from 0-1, preferably 0-0.5 equivalents, calculated with respect to the amount of salt with formula (2). Higher

amounts of catalyst are also possible, but will normally have no extra advantageous effect. Preferably the amount of catalyst, if any, will be between 0.05 and 0.2 equivalents calculated with respect to the salt with formula (2). Suitable catalysts are the catalysts generally known to accelerate acid chloride formation, for instance

5 dimethylformamide (DMF) and N-methylpyrrolidone (NMP).

The conversion of the acid chloride into the ester with formula (1) is carried out in the presence of an alcohol with formula R^2OH . The amount of alcohol with formula R^2OH is not very critical and preferably is between 1 and 15 equivalent calculated with respect to the amount of salt with formula (2), more preferably between

10 2 and 13, most preferably between 3 and 6. Surprisingly it has been found that even t-butyl esters can be prepared with high yield using a relatively low amount of t-butyl alcohol.

The conversion of the acid chloride into the ester with formula (1) is carried out in the presence of NMM. In practice a small amount of NMM, efficient to

15 catch eventually remaining free HCl, for instance 1.5 to 2.5, preferably 1.8 to 2.0 equivalents calculated with respect to the amount of salt with formula (2) is applied. When a large excess of acid chloride forming agent is used, preferably higher amounts of NMM are used, and when a lower excess of acid chloride forming agent is used, preferably lower amounts of NMM are used.

The acid chloride formation reaction preferably is carried out at a temperature between $-30^{\circ}C$ and $60^{\circ}C$, more preferably between $20^{\circ}C$ and $50^{\circ}C$. The conversion of the acid chloride into the ester with formula (1) preferably is carried out at a temperature between $20^{\circ}C$ and $80^{\circ}C$, more preferably between $20^{\circ}C$ and $50^{\circ}C$.

20

The process of the present invention may be carried out in one step.

25 Preferably first the salt with formula (2) is converted into the corresponding acid chloride, and subsequently the acid chloride is contacted with the alcohol with formula R^2OH and NMM. In a particularly preferred embodiment the acid chloride formed is quenched with NMM and the alcohol with formula R^2OH .

The product with formula 1, wherein R^1 represents a leaving group may subsequently be converted into the corresponding compound wherein R^1 represents an acyloxy group. This can be achieved in a manner known per se, for instance by reaction with an acyloxylating agent for instance a carboxylic or sulphonic acid, a quaternary ammonium or phosphonium salt, a carboxylic or sulphonic acid quaternary ammonium or phosphonium salt or a combination thereof. Preferably a

30 combination of a quaternary phosphonium salt and a carboxylic or sulphonic acid salt is used as the acyloxylating agent.

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Subsequently the compound with formula 1, wherein R¹ represents an acyloxy group can be converted in the corresponding compound wherein R¹ represents a hydroxy group, for instance by subjecting it to solvolysis in the presence of a base. Suitable bases are, for instance, alkali (earth) metal hydroxides or carbonates or organic bases, for instance alkali (earth) metal carboxylic acids, for instance acetates, ammonia, pyridines, amines, for instance triethylamine and the like.

The invention will be elucidated by the following examples.

Example I

10 1864 g of an aqueous solution of the (4R-cl)- (6-chloromethyl)-2,2-dimethyl-1,3-dioxane-4-yl-acetic acid, sodium salt (3.31 moles) and 4.8 L of toluene were mixed and water was removed by azeotropic distillation under reduced pressure. Subsequently, 870 g of fresh toluene were added and removed by distillation. To the obtained suspension was added 33.4g of NMP. Then 588 g of oxalyl chloride were
15 added while maintaining the temperature at 20 °C. The resulting mixture was stirred for 6 hours at 20-25 °C and then slowly added to a mixture of 879 g of t-butanol and 836 g of N-methyl morpholine. After stirring for 1 hour, 3986 g of an 8% (w/w) aqueous NaOH solution was added and the resulting mixture stirred for 1.5 hours at 40 °C. After washing the organic phase with 3300 g of water, 3064 g of a toluene solution of the
20 desired t-butyl ester was obtained, corresponding to 751 g (81%) of product.

Example II

25 In a 100 ml HEL Vessel with 4 blade stirrer 8.0 g (4R-cl)- (6-chloromethyl)-2,2-dimethyl-1,3-dioxane-4-yl-acetic acid, sodium salt (92.4%; 30 mmol) was suspended in 41 g toluene and 0.3 g NMP (3 mmol). In 1h 4.5 g (36 mmol) oxalylchloride was dosed at a temperature of 15-20°C. The reaction mixture (50 g) was stirred for 2.5 hours. The reaction mixture was split into 2 parts: Part A (23.83 g) and part B (24.25 g). Part A of the reaction mixture was dosed during 1 h. to a mixture of
30 22.2 g (20 eq.) t-butanol and 3.0 g (2 eq.) NMM at 25°C. The reaction mixture was stirred overnight and analyzed by GC. The yield of the t-butyl ester was 88%.

XX 10

Examples III-V

Following the same procedure as described in Example I, the ethyl, isopropyl and n-hexyl esters, respectively, are prepared wherein instead of 4 eq. butanol, now 4 eq. ethanol, 4 eq. isopropanol and 4 eq. n-hexanol, respectively is used. The yield of the desired ethyl, isopropyl and n-hexyl ester was 89 mol%, 88 mol% and 84 mol% respectively, calculated with respect to the sodium salt starting material.

Example VI

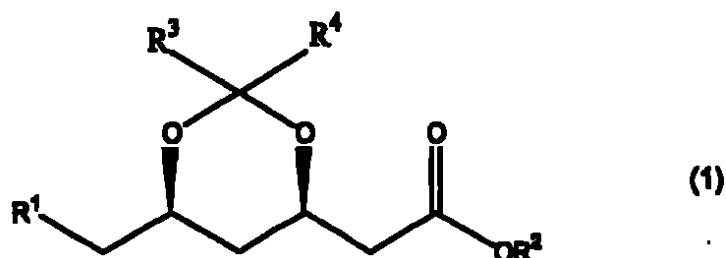
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A mixture of 35.0 g of t-butyl (4R-cis)-(6-chloromethyl)-2,2-dimethyl-1,3-dioxane-4-yl-acetate, 14.8 g of tetrabutyl phosphonium bromide, 18.0 g of potassium acetate and 5.9 g of toluene were heated to 105 °C under reduced pressure. After 22 hours at this temperature the reaction mixture was cooled to ambient temperature after which 400 g of heptane and 350 g of water were added. The organic phase was washed with 150 g of water and subsequently treated with 3.0 g of activated carbon. After filtration of the carbon, the solution was concentrated and subsequently cooled to -10 °C after which crystallised product was isolated by means of filtration. Yield 24.9 g (76%) of a white crystalline material

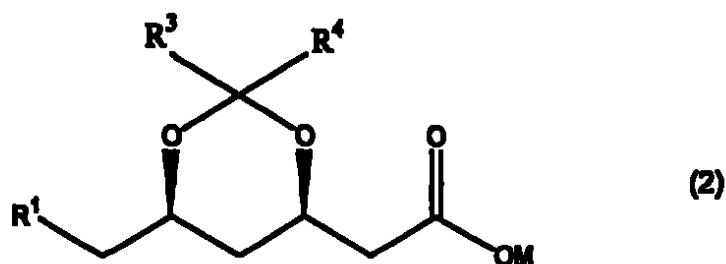
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CLAIMS

1. Process for the preparation of an ester of formula (1),



wherein R¹ represents a leaving group, CN, OH or a COOR⁵ group, R³ and R⁴ each independently represent a 1-3 C alkyl group, and R² and R⁵ each independently represent an ester residue, wherein the corresponding salt with formula (2),



wherein M represents H or an alkali (earth) metal in an inert solvent is contacted with an acid chloride forming agent to form the corresponding acid chloride, and the acid chloride is contacted with an alcohol with formula R²OH in the presence of N-methyl-morpholine.

2. Process according to claim 1, wherein M represents an alkali metal.
3. Process according to claim 1 or 2, wherein R² represents an alkyl group.
4. Process according to claim 3, wherein R² represents a t-butyl group.
5. Process according to any one of claims 1-4, wherein the acid chloride forming agent is oxalylchloride.
6. Process according to any one of claims 1-5, wherein the acid chloride formation is performed in the presence of a catalyst.
7. Process according to any one of claims 1-6, wherein the amount of alcohol

with formula R^2OH is between 3 and 6 equivalents calculated with respect to the amount of salt with formula (2).

- 5 8. Process according to any one of claims 1-7, wherein first the salt with formula (2) is converted into the corresponding acid chloride and subsequently the acid chloride is contacted with the alcohol with formula R^2OH and N-methyl-morpholine.
9. Process according to claim 8, wherein the acid chloride is quenched with the alcohol with formula R^2OH and N-methyl-morpholine.
- 10 10. Process according to any one of claims 1-9, wherein R^1 represents a leaving group, and wherein the ester of formula 1 wherein R^1 represents a leaving group is subsequently converted into the corresponding ester with formula 1 wherein R^1 represents an acyloxy group.
- 15 11. Process according to claim 10, wherein first an ester of formula 1 wherein R^1 represents an acyloxy group is prepared and subsequently the ester of formula 1 is converted into the corresponding compound with formula 1 wherein R^1 represents OH.

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/NL 03/00435A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D319/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02 06266 A (MINK DANIEL ; DSM NV (NL); KOOISTRA JACOB HERMANUS MATTHE (NL); MUL) 24 January 2002 (2002-01-24) page 5, line 4 -page 6, line 31; claim 8; example VII ---	1-11
A	WO 00 68221 A (EGYT GYOGYSZERVEGYESZETI GYAR ; VERECZKEYNE DONATH GYOERGYI (HU); B) 16 November 2000 (2000-11-16) page 7, paragraph 4 ---	1-11
A	GB 885 516 A (ARTHUR HENRY CLARKSON) 28 December 1961 (1961-12-28) page 1: left-hand column, paragraph 4 page 2: right-hand column, last paragraph --- -/--	1-11

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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Date of the actual completion of the international search

26 August 2003

Date of mailing of the international search report

12/09/2003

Name and mailing address of the ISA

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Stroeter, T

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/NL 03/00435

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MARCH J: "ALIPHATIC NUCLEOPHILIC SUBSTITUTION" ADVANCED ORGANIC CHEMISTRY. REACTIONS, MECHANISMS, AND STRUCTURE, NEW YORK, JOHN WILEY & SONS, US, 1992, page 392 XP002217003 ISBN: 0-471-60180-2 chapter 0-20 page 392	1-11
A	MURPHY C F, KOEHLER R. E.: "CHEMISTRY OF CEPHALOSPORIN ANTIBIOTICS. XVIII." J. ORG. CHEM., vol. 35, no. 7, 1970, pages 2429-2430, XP002252465 right-hand column, first paragraph	1-11

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[Handwritten mark]

INTERNATIONAL SEARCH REPORT

Internal application No
PCT/NL 03/00435

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 0206266	A	24-01-2002	NL	1015744 C2	22-01-2002
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			CA	2415963 A1	24-01-2002
			CZ	20030163 A3	14-05-2003
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			NO	20030025 A	03-01-2003
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			PL	351145 A1	24-03-2003
			SK	15842001 A3	04-04-2002
			GB 885516	A	28-12-1961

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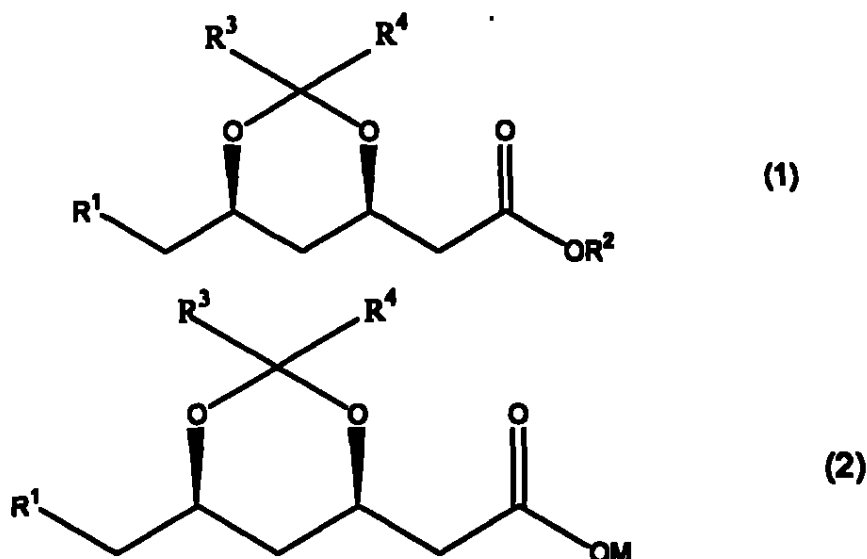
PCT

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- (21) Número de Solicitud Internacional: PCT/NL03/00435 (74) Apoderado: JACOBS, Monique, Sophie, Nicole; DSM Intellectual Property, P.O. Box 9, NL-6160 MA Geleen (NL)
- (22) Fecha de Entrega Internacional: 12 de Junio de 2003 (12.06.2003) (81) Estados Designados (nacionales): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HY, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UAM, UG, UZ, VN, YU, ZA, ZM, ZW.
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- (30) Datos de la Prioridad: 02100715.8 17 de Junio de 2002 (17.06.2002) EP (84) Estados Designados (regionales): Patente ARIPO (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Patente Euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente europea (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), Patente OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
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(54) Título: PROCESO PARA LA PREPARACION DE ESTERES DE ACIDO DIOXAN ACETICO



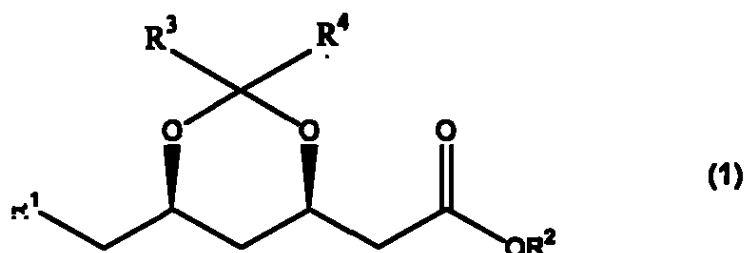
(57) Resumen: Proceso para la preparación de un éster de fórmula (1), en donde R¹ representa un grupo saliente, CN, OH, o un grupo COOR⁵, R³ y R⁴ representan cada uno independientemente un grupo C1-3 alquilo, y R² y R⁵ representan cada uno independientemente un residuo de éster, en donde la sal correspondiente de fórmula (2), en donde M representa H o un metal alcalino (támo) en un solvente inerte es puesta en contacto con el agente formador del cloruro ácido para formar al cloruro ácido correspondiente, y el cloruro ácido es puesto en contacto con un alcohol con fórmula R²OH en presencia de N-metilmorfolina. Preferiblemente M representa un metal alcalino, y R² representa un grupo alquilo, particularmente un grupo t-butilo. (1) (2).

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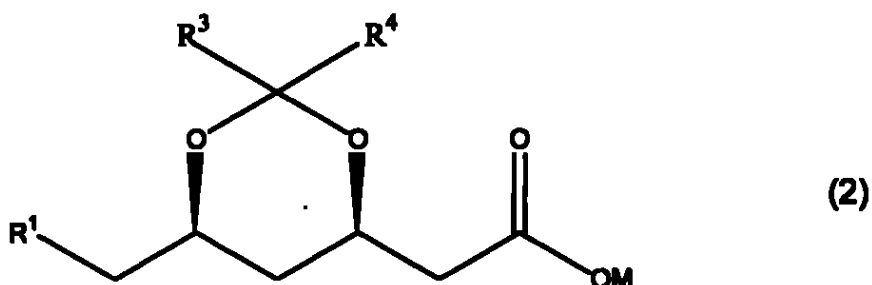
Para los códigos de dos letras y otras abreviaturas, referirse a las "Notas de Guía sobre Códigos y Abreviaturas" que aparece al comienzo de cada emisión regular de la Gaceta del PCT.

PROCESO PARA LA PREPARACION DE ESTERES DE ACIDO DIOXAN
ACETICO

Esta invención se relaciona con un proceso para la preparación de un éster de fórmula (1)



en donde R¹ representa un grupo de salida, CN, OH o un grupo COOR⁵, R³ y R⁴ representan cada uno independientemente un grupo C1-C3 alquilo y R² y R⁵ representan cada uno independientemente un residuo de éster, en donde la sal correspondiente con la fórmula (2)



en donde M representa H o un metal alcalino (terreo) en un solvente inerte es puesto en contacto con un agente formador de un cloruro ácido para formar el cloruro ácido correspondiente, y el cloruro ácido es puesto en contacto con un alcohol de fórmula R²OH en presencia de N-metil morfolina (NMM).

En el arte se conocen muchos procesos para la preparación de ésteres, por ejemplo la preparación de ésteres por medio de la formación del cloruro ácido. Sin embargo, era de esperarse que tales procesos no llevaran a altos rendimientos debido a la falta de estabilidad del presente compuesto bajo condiciones ácidas.

El objeto de la presente invención es proporcionar un proceso para la preparación de ésteres con un proceso más robusto de alto rendimiento, incluso a gran escala y con concentraciones relativamente altas.

Sorpresivamente se ha encontrado que incluso los ésteres estéricamente impedidos que son difíciles de obtener en esterificaciones como los t-butil ésteres de moléculas inestables en ácido de fórmula (1), pueden obtenerse con un alto rendimiento en un proceso fácilmente reproducible.

Con el proceso de acuerdo con la invención los ésteres de fórmula (1) que son inestables bajo condiciones ácidas, por ejemplo a $\text{pH} < 4$, pueden ser preparados con un alto rendimiento.

R^1 representa un grupo saliente, CN, OH o un grupo COOR^5 en donde R^5 representa un residuo de éster, por ejemplo un grupo alquilo con por ejemplo 1 - 6 átomos de carbono, o un grupo arilo con por ejemplo 6 - 12 átomos de carbono. Por definición un grupo saliente es un grupo que puede ser reemplazado fácilmente, por ejemplo un halógeno, como Cl, Br o I; un grupo tosilato; un grupo mesilato; un grupo aciloxilo, con, por ejemplo, 1 - 6 átomos de carbono en particular un grupo acetoxilo; un grupo fenacetiloxilo; un grupo alcoxilo con, por ejemplo, 1 - 6 átomos de carbono o un grupo (hetero) ariloxilo con, por ejemplo, 6 - 12 átomos de carbono. Preferiblemente R^1 representa Cl.

R^2 representa un residuo de éster, preferiblemente un grupo alquilo, por ejemplo un grupo alquilo con 1 - 6 átomos de carbono o un grupo arilo, por ejemplo un grupo arilo con 6 - 12 átomos de carbono, en particular un grupo metilo, etilo, propilo, isobutilo o t-butilo. Un grupo importante de ésteres que puede prepararse con el proceso de acuerdo con la invención son los t-butil ésteres.

R^3 y R^4 representan cada uno independientemente un grupo C1-C3 alquilo, por ejemplo un grupo metilo o etilo. Preferiblemente R^3 y R^4 ambos representan metilo.

M en la fórmula (2) puede seleccionarse del grupo de H, metales alcalinos, por ejemplo litio, sodio, potasio y metales alcalino-térreos, por ejemplo magnesio o calcio. Preferiblemente M representa sodio o potasio.

El agente formador del cloruro ácido puede seleccionarse del grupo de reactivos que generalmente se conoce como tal. Ejemplos apropiados de agentes formadores de cloruro ácido son el cloruro de oxalilo, cloruro de tionilo, PCl_3 , PCl_5 y POCl_3 . Preferiblemente el agente formador de cloruro ácido es usado en un exceso relativo a la cantidad de sal con fórmula (2), por ejemplo entre 1 y 3 equivalentes, más preferiblemente entre 1.2 y 1.8 equivalentes.

Si se desea, en la formación del cloruro ácido también puede estar presente un catalizador. La cantidad de catalizador puede por ejemplo variar desde 0 - 1, preferiblemente de 0 - 0.05 equivalentes, calculados respecto a la cantidad de sal de fórmula (2). También son posibles cantidades más altas de catalizador, pero normalmente no tendrá un efecto ventajoso adicional. Preferiblemente la cantidad de catalizador, si hay, estará entre 0.05 y 0.2 equivalentes calculados respecto a la sal de fórmula (2). Los catalizadores apropiados son los catalizadores generalmente conocidos por acelerar la formación de cloruro ácido, por ejemplo dimetilformamida (DMF) y N-metilpirrolidona (NMP).

La conversión de cloruro ácido en el éster con fórmula (1) se lleva a cabo en presencia de un alcohol con fórmula R^2OH . La cantidad de alcohol con fórmula R^2OH no es muy crítica y preferiblemente se encuentra entre 1 y 15 equivalentes calculados respecto a la cantidad de sal con fórmula (2), más preferiblemente entre 2 y 13, más preferiblemente entre 3 y 6. Sorpresivamente se ha encontrado que incluso los t-butil ésteres pueden prepararse con un alto rendimiento usando una cantidad relativamente baja de t-butil alcohol.

La conversión del cloruro ácido en el éster con la fórmula (1) se lleva a cabo en presencia de NMM. En la práctica se aplica una cantidad pequeña de NMM, eficiente para atrapar HCl eventualmente libre, por ejemplo 1.5 a 2.5, preferiblemente 1.8 a 2.0 equivalentes calculados respecto a la cantidad de sal con fórmula (2). Cuando se usa un gran exceso de agente formador de cloruro ácido, preferiblemente se utilizan mayores cantidades de

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NMM, y cuando se usa una cantidad menor en exceso de agente formado de cloruro ácido, preferiblemente se utilizan cantidades más bajas de NMM.

La reacción de formación de cloruro ácido preferiblemente se lleva a cabo a una temperatura entre -30 y 60°C , más preferiblemente entre 20 y 50°C . La conversión del cloruro ácido en el éster de fórmula (1) preferiblemente se lleva a cabo a una temperatura entre 20 y 80°C , más preferiblemente entre 20 y 50°C .

El proceso de la presente invención puede llevarse a cabo en un solo paso. Preferiblemente primero la sal con fórmula (2) es convertida a en el cloruro ácido correspondiente, y subsiguientemente el cloruro ácido es puesto en contacto con el alcohol de fórmula R^2OH y el NMM. En una modalidad particularmente preferida el cloruro ácido formado es enfriado con el NMM y el alcohol de fórmula R^2OH .

El producto de fórmula 1, en donde $\text{R}1$ representa un grupo saliente puede convertirse subsiguientemente en el compuesto correspondiente en donde $\text{R}1$ representa un grupo alcóxido. Esto puede lograrse en una manera conocida per se, por ejemplo por reacción con un agente alcóxidante por ejemplo un ácido carboxílico o sulfónico, una sal cuaternaria de amonio o de fosonio, una sal cuaternaria de ácido carboxílico o sulfónico de amonio o fosonio o una combinación de los mismos. Preferiblemente se utiliza una combinación de una sal cuaternaria de fosonio y una sal de ácido carboxílico o sulfónico como agente alcóxidante.

Subsiguientemente el compuesto de fórmula 1, en donde $\text{R}1$ representa un grupo alcóxido que puede convertirse en el compuesto correspondiente en donde $\text{R}1$ representa un grupo un grupo hidróxido, por ejemplo sometiéndolo a solvolisis en presencia de una base. Las bases adecuadas son, por ejemplo, hidróxidos de metales alcalinos (terreos) o carbonatos o sales orgánicas, por ejemplo ácidos carboxílicos de metales alcalinos (terreos), por ejemplo acetatos, amoniaco, piridinas, aminas, por ejemplo trietilamina y semejantes.

La invención será elucidada de los siguientes ejemplos.

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B

Ejemplo 1

1864 g de una solución acuosa de la sal de sodio del ácido (4R-cis)-(6-clorometil)-2,2-dimetil-1,3-dioxan-4-il acético (3.31 moles) y 4.8 L de tolueno se mezclaron y se removió el agua por destilación azeotrópica bajo presión reducida. Subsiguientemente, se agregaron 870 g de tolueno fresco y se removieron por destilación. A la suspensión obtenida se le agregaron 33.4 g de NMP. Luego se agregaron 588 g de cloruro de oxalilo mientras se mantenía la temperatura a 20°C. La mezcla resultante se agitó por 6 horas a 20-25 °C y luego se agregó lentamente a una mezcla de 979 g de t-butanol y 836 g de N-metil morfolina. Después de agitar por 1 hora, se agregaron 3966 g de una solución acuosa al 8% (v/v) de NaOH y la mezcla resultante se agitó por 1.5 horas a 40°C. Después de lavar la fase orgánica con 3300 g de agua, se obtuvieron 3084 g de una solución del t-butil éster en tolueno, lo que corresponde a 751 g (81%) de producto.

Ejemplo II

En un recipiente HEL de 100 mL con agitador de 4 aspas se suspendieron 8.0 g de sal de sodio de ácido (4R-cis)-(6-clorometil)-2,2-dimetil-1,3-dioxan-4-il acético (92.4%; 30 mmol) en 41 g de tolueno y 0.3 g de NMP (3 mmol). En una hora se dosificaron 4.5 g (36 mmol) de cloruro de oxalilo a una temperatura de 15 - 20°C. La mezcla de la reacción (50 g) se agitó por 2.5 horas. La mezcla de la reacción se partió en 2 partes: Parte A (23.83 g y parte B (24.25 g). La parte A de la reacción se dosificó durante 1 hora a una mezcla de 22.2g (20 eq.) de t-butanol y 3.0 g (2 eq.) de NMM a 25°C. La mezcla de la reacción se agitó durante la noche y se analizó por GC. El rendimiento de t-butil éster fue del 88%.

Ejemplos III - V

Siguiendo el mismo procedimiento descrito en el ejemplo I, se prepararon los ésteres de etilo, isopropilo y n-hexilo, respectivamente, en donde en lugar de 4 eq. de butanol ahora se usan 4 eq. de etanol, 4 eq. de isopropanol y 4 eq. de n-hexanol, respectivamente. El rendimiento del éster de etilo, isopropilo y n-hexilo deseados fue de 89% molar, 88% molar y 84% molar respectivamente, calculado respecto a la sal de sodio del material inicial.

Ejemplo VI

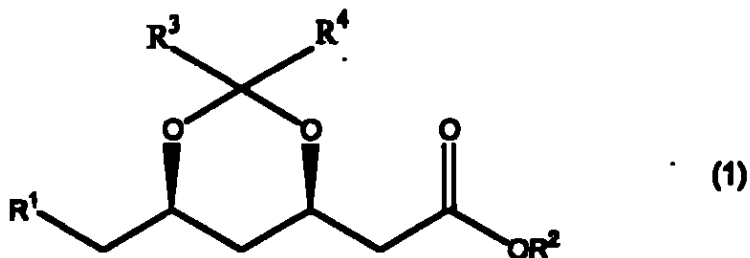
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Una mezcla de t-butil (4R-cis)-(6-clorometil)-2,2-dimetil-1,3-dioxan-4-il-acetato, 14.8 g de bromuro de tetrabutil fosfonio, 16.0 g de acetato de potasio y 5.9 g de tolueno se calentaron a 105 °C bajo presión reducida. Después de 22 horas a esta temperatura la mezcla de la reacción se enfrió a temperatura ambiente tras lo cual se agregaron 400 g de heptano y 350 g de agua. La fase orgánica se lavó con 150 g de agua y se trató subsiguientemente con 3.0 g de carbón activado. Después de filtrar el carbón, se concentró la solución y subsiguientemente se enfrió a -10°C tras lo cual se aisló el producto cristalizado por medio de filtración. Se obtuvo un rendimiento de 24.9 g (76%) de material cristalino blanco.

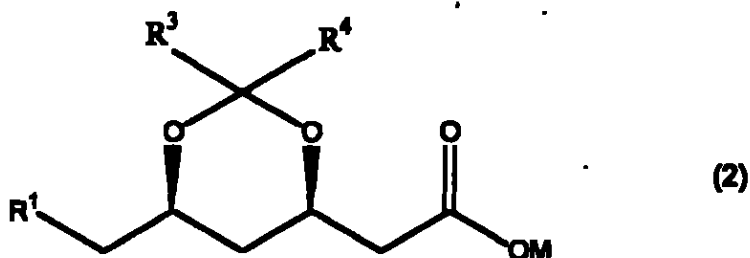
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REIVINDICACIONES

1. Proceso para la preparación de un éster de fórmula (1),



En donde R1 representa un grupo saliente, CN, OH o un grupo COOR5, R3 y R4 representan independientemente cada uno un grupo C1-3 alquilo, 5 R2 y R5 representan cada uno independientemente un residuo de éster, en donde la sal correspondiente con fórmula (2)



en donde M representa H o un metal alcalino (térreo) en un solvente inerte es puesta en contacto con un agente formador de cloruro ácido, y el cloruro ácido es puesto en contacto con un alcohol de fórmula R²OH en presencia de N-metil-morfolina.

2. El proceso de acuerdo con la reivindicación 1, en donde M representa un metal alcalino.
3. EL proceso de acuerdo con la reivindicación 1 o 2, en donde R² representa un grupo alquilo.
4. El proceso de acuerdo con la reivindicación 3, en donde R2 representa un grupo t-butilo.

5. El proceso de acuerdo con cualquiera de las reivindicaciones 1 - 4, en donde el agente formador de cloruro ácido es cloruro de oxalilo.
6. El proceso de acuerdo con cualquiera de las reivindicaciones 1 - 5, en donde la formación del cloruro ácido se lleva a cabo en presencia de un catalizador.
7. El proceso de acuerdo con las reivindicaciones 1 - 6, en donde la cantidad de alcohol con fórmula R^2OH está entre 3 y 6 equivalentes calculados respecto a la sal de fórmula (2).
8. El proceso de acuerdo con cualquiera de las reivindicaciones 1 - 7, en donde primero la sal con la fórmula (2) es convertida en el cloruro ácido correspondiente y subsiguientemente el cloruro ácido es puesto en contacto con el alcohol de fórmula R^2OH y N-metil-morfolina.
9. El proceso de acuerdo con la reivindicación 8, en donde el cloruro ácido es enfriado con el alcohol de fórmula R^2OH y la N-metil-morfolina.
10. El proceso de acuerdo con cualquiera de las reivindicaciones 1 - 9, en donde R^1 representa un grupo saliente, y en donde el éster de fórmula 1 en donde R^1 representa un grupo saliente es subsiguientemente convertido en el éster correspondiente con fórmula 1 en donde R^1 representa un grupo aciloxilo.
11. El proceso de acuerdo con la reivindicación 10, en donde primero se prepara un éster de fórmula 1 donde R^1 representa un grupo aciloxilo y subsiguientemente el éster de fórmula 1 es convertido en el compuesto correspondiente con fórmula 1 en donde R^1 representa OH.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 20916WO	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEAA/16)	
International application No. PCT/NL 03/00495	International filing date (day/month/year) 12.06.2003	Priority date (day/month/year) 17.06.2002
International Patent Classification (IPC) or both national classification and IPC C07D319.06		
Applicant DSM IP ASSESTS B.V. 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 5 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 70.15 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 opinion II ☐ Priority III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Rule 66.2(a)(ii) 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 02.12.2003	Date of completion of this report 11.11.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80289 Munich Tel: +49 89 2399-0 Fax: +49 89 2399-4466	Authorized Officer Stroeter, T Telephone No. +49 89 2399-8055 	

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**International application No. **PCT/NL 03/00435****I. Basis of the report**

1. With regard to the elements of the international application (*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 not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*)

Description, Pages

1-5 as originally filed

Claims, Numbers

1-11 as originally filed

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 the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 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, sheets:

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 (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**International application No. **PCT/NL 03/00435****V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement****1. Statement**

Novelty (N)	Yes: Claims	1-11
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-11
Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	

2. Citations and explanations

see separate sheet

INTERNATIONAL PRELIMINARY

International application No. PCT/NL 03/00435

EXAMINATION REPORT - SEPARATE SHEET**Re item V****Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement****1 Prior art documents**

Reference is made to the following documents. The given numbering will be adhered to in the rest of the procedure:

- D1: WO 02/06286 A (MINK DANIEL ;DSM NV (NL); KOOISTRA JACOB HERMANUS MATTHE (NL); MUL) 24 January 2002
- D2: WO 00/68221 A (EGYT GYOGYSZERVEGYESZETI GYAR ;VERECZKEYNE DONATH GYOERGYI (HU); B) 16 November 2000
- D3: GB 885 516 A (ARTHUR HENRY CLARKSON) 28 December 1961
- D4: MARCH J: "ALIPHATIC NUCLEOPHILIC SUBSTITUTION" ADVANCED ORGANIC CHEMISTRY. REACTIONS, MECHANISMS, AND STRUCTURE, NEW YORK, JOHN WILEY & SONS, US, 1992, page 392, XP002217003 ISBN: 0-471-60180-2
- D5: MURPHY C F, KOEHLER R. E.: "CHEMISTRY OF CEPHALOSPORIN ANTIBIOTICS. XVIII." J. ORG. CHEM., vol. 35, no. 7, 1970, pages 2429-2430, XP002252465

2 Novelty (Article 33(2) PCT)

The most related prior art appears to be D1 disclosing on page 5, last paragraph, a process wherein a carboxylic acid derivative of present formula (2) is transformed into the corresponding acid chloride, e.g. by use of oxalylchloride. Said acid chloride is then converted to the ester with a tertiary alcohol in the presence of a base. D1 also refers to the present stereochemistry (see page 2). Therefore D1 is a generic disclosure of the present invention but fails to mention the specific base N-methylmorpholine (NMM) as a base in the second reaction step. Consequently, the present process of claim 1 represents a novel selection of what has been disclosed in D1. Claims 1-11 are novel by consequence.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/NL 03/00435

3 Inventive step (Article 33(3) PCT)

The selection of NMM as a base appears to be an obvious solution to the problem of providing an alternative process for the preparation of the esters of formula (1). Reactions of the Schotten-Baumann type are widely used in organic chemistry whenever esters have to be prepared. The presence of a base is a necessary feature in these reactions (D3, D4). It is well known that aprotic, non-nucleophilic and weak bases are preferred in order to avoid the formation of amides, e.g. dimethylaminopyridine (D1), NMM (D3), pyridine (D3, D4) or triethylamine (D5). Therefore, in the absence of a specific unexpected effect, the present subject-matter of claims 1-11 lacks an inventive step.

Please note, that D2, page 7, 4th paragraph already states that "...ketale group would be resistant to organic acids under the reaction conditions used..." and thus no surprising effect can be assigned to the stability of the present ketals under acidic conditions.

4 Industrial applicability (Article 33(4) PCT)

The subject-matter of the present set of claims 1 to 11 is in accordance with the requirements of Article 33(4) PCT.

* * * ERROR REPORT (2. DEC. 2004 14:36) *

TTI GLOBAL IP PATENTS

FILE	PERS. NAME	ADDRESS	MODE	TIME	PAGE	RESULT
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PAGE NOT RECEIVED

P. 5

: BATCH
M : MEMORY
S : STANDARD
IS : REMOTE TRANSFER

C : CONFIDENTIAL
L : SEND LATER
D : DETAIL
B : FAX ON DEMAND

S : TRANSFER
O : FORWARDING
F : FINE
A : PC

P : POLLING
E : ECM
J : REDUCTION
N : PC DIRECT

37 32

**TRATADO SOBRE COOPERACIÓN INTERNACIONAL
EN MATERIA DE PATENTES**

PCT

INFORME DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 36 y Regla 70 PCT)

No. de Expediente del Solicitante o Apoderado 20916WO	PROCEDIMIENTO POSTERIOR Véase comunicación sobre el envío del Informe de examen preliminar internacional (Formulario PCT/IPEA/416)	
No. Solicitud Internacional PCT/NL 03/00435	Fecha Internacional de Presentación (día/mes/año) 12.06.2003	Fecha de Prioridad (día/mes/año) 17.06.2002
Clasificación Internacional de Patente (IPC) o Clasificación Nacional e IPC C07D 19/08		
Solicitante DSM IP ASSESTS B.V. y colaboradores		

1.	Este Informe de examen preliminar internacional fue elaborado por la Oficina Encargada del Examen Preliminar Internacional y se envía al solicitante según Artículo 36.
2.	Este INFORME comprende un total de 5 hojas, inclusive esta portada ☐ Además se adjuntan ANEXOS al informe; en este caso se trata de hojas con descripciones, reivindicaciones y/o dibujos, que se modificaron y que sirven de base a este Informe, y/o hojas con correcciones efectuadas por esta oficina (véase Regla 70.16 y Sección 807 de las Instrucciones administrativas al PCT). Estos anexos comprenden en total de hojas.
3.	Este Informe contiene datos con respecto a los siguientes puntos: I ☒ Base del Informe II ☐ Prioridad III ☐ Sin elaboración de un dictamen sobre novedad, actividad inventiva y posibilidad de aplicación industrial IV ☐ Uniformidad deficiente de la invención V ☒ Declaración justificada según Artículo 35(2) con respecto a la novedad, la actividad inventiva y la posibilidad de aplicación industrial; documentos y explicaciones que sustentan esta declaración VI ☐ Ciertos documentos enumerados VII ☐ Ciertas deficiencias del registro internacional VIII ☐ Ciertas observaciones relacionadas con la solicitud internacional

Fecha de presentación de la petición 02.12.2003	Fecha de la preparación de este informe 11.11.2004
Nombre y dirección postal de la IPEA Oficina Europea de Patentes D-80298 Munich Tel. +49 89 2399-0 Tx: 523656 empu d Fax: +49 89 2399 - 4465	Empleado Autorizado Stroeter, T Teléfono No. +49 89 2399-8088

I. Base para este Informe.

1. Respecto a los elementos de la solicitud internacional (Las hojas de reemplazo que han sido entregadas a la oficina receptora en respuesta a una invitación bajo el Artículo 14 se referencian en éste reporte como "entregadas originalmente" y nos anexadas a este reporte ya que no contienen enmendaduras (Reglas 70.16 y 70.17)):

Descripción, páginas

1 – 5 como se entregaron originalmente

Reivindicaciones, No.:

1 – 1 como se entregaron originalmente

2. Respecto al idioma, todos los elementos anteriormente marcados estaban disponibles o fueron suministrados a esta oficina en el idioma en el que se entregó la solicitud internacional, a menos que se diga lo contrario en este punto. Estos elementos estaban disponibles o fueron entregados a esta oficina en el siguiente idioma _____ los cuales son

- ☐ El idioma de la traducción entregada para propósitos de la búsqueda internacional (Regla 23.1 (b)).
- ☐ El idioma de publicación de la solicitud internacional (bajo la Regla 48.3 (b)).
- ☐ El idioma de la traducción entregada para propósitos del examen preliminar internacional (bajo las Reglas 55.2 y/o 55.3)

3. respecto a cualquier secuencia de nucleótido y/o aminoácidos divulgados en esta solicitud internacional, el examen preliminar internacional se realizó sobre la base de la secuencia:

- ☐ contenida en la solicitud en forma impresa
- ☐ entregada junto con la solicitud internacional en una forma legible en un computador
- ☐ suministrada subsiguientemente a esta oficina de forma escrita
- ☐ suministrada subsiguientemente a esta oficina en forma legible en un computador
- ☐ la declaración que la secuencia escrita suministrada no va más allá de lo divulgado en la solicitud internacional como se entregó ha sido suministrada
- ☐ La declaración que la información registrada en la forma legible a computador es idéntica a la secuencia escrita ha sido suministrada.

4. ☐ Las correcciones han resultado en la cancelación de:

- ☐ la descripción, páginas:
- ☐ las reivindicaciones, Nos:
- ☐ los dibujos, hojas:

5. ☐ Este informe ha sido admitido como si (algunas de) las correcciones no hubieran sido hechas, ya que se considera que estas van más allá de la divulgación preliminar, como se indica el Apartado Suplementario (Regla 70.2 (c)):

(Cualquier hoja de reemplazo que contenga dichas enmiendas debe ser referenciada bajo el asunto 1 y anexada a este reporte.)

6. Observaciones adicionales, de ser necesarias:

34.

INFORME DEL EXAMEN

PRELIMINAR INTERNACIONAL

No de Solicitud Internacional

PCT/NL 03/00435

V. Declaración concluyente bajo el Artículo 35(2) con respecto a la novedad, el nivel inventivo o la aplicabilidad industrial; las citas y explicaciones que sustentan dicha declaración

1. DECLARACIÓN

Novedad (N)	Si: Reivindicaciones 1 – 11
	No: Reivindicaciones
Nivel Inventivo (IS)	Si: Reivindicaciones
	No: Reivindicaciones 1 - 11
Aplicabilidad Industrial (IA)	Si: Reivindicaciones 1 – 11
	No: Reivindicaciones

2. CITAS Y EXPLICACIONES

Ver hoja aparte

Re Item V

Declaración justificada bajo el Artículo 35(2) respecto a la novedad, el nivel inventivo y la aplicabilidad industrial; citas y explicaciones que sustentan tal declaración.

1 Documentos del arte previo

Se hace referencia a los siguientes documentos. Los números dados serán mantenidos en el resto del procedimiento:

- D1: WO 02/06266 A (MINK DANIEL; DSM NV (NL); KOOISTRA JACOB HERMANUS MATTHE (NL); MUL) 24 de enero de 2002.
- D2: WO 00/68221 A (EGYT GYOGYSZERVEGYESZETI GYAR; VERECZKEYNE DONATH GYOERGYI (HU); B) 16 de noviembre de 2000.
- D3: GB 885 516 A (ARTHUR HENRY CLARKSON) 28 de diciembre de 1961.
- D4: MARCH J. "ALIPHATIC NUCLEOPHILIC SUBSTITUTION" ADVANCED ORGANIC CHEMISTRY, REACTIONS, MECHANISMS, AND STRUCTURE, NEW YORK, JOHN WILEY & SONS, US, 1982, página 392, XP002217003 ISBN: 0-471-80180-2.
- D5: MURPHY C F, KOEHLER R. E.: "CHEMISTRY OF CEPHALOSPORIN ANTIBIOTICS. XVIII" J. ORG. CHEM., vol. 35, no. 7, 1970, páginas 2429 - 2430, XP002252465.

2 Novedad (Artículo 33(2) del PCT)

El arte previo más relacionado parece ser D1 que divulga en la página 5, último párrafo, un proceso en donde un ácido carboxílico derivativo de la presente fórmula (2) es transformado en su cloruro ácido correspondiente, por ejemplo por uso de cloruro de oxalilo. Dicho cloruro ácido luego es convertido en un éster con un alcohol terciario en presencia de una base. D1 también se refiere a la estereoquímica presente (ver página 2). Por lo tanto D1 es una divulgación genérica de la presente invención pero falla en mencionar la base N-metilmorfolina (NMM) como base en el segundo paso de la reacción. Consecuentemente, el presente proceso de la reivindicación 1 representa una selección novedosa de los que ha sido divulgado en D1. Las reivindicaciones 1 - 11 son por consecuencia novedosas.

3 Nivel Inventivo (Artículo 33(3) del PCT)

La selección del NMM como base parece ser una solución obvia al problema de proporcionar un proceso alternativo para la preparación de ésteres de fórmula (1). Las reacciones del tipo Schotten-Baumann son ampliamente usadas en la química orgánica dondequiera que se deban preparar ésteres. La presencia de una base es una característica necesaria en estas reacciones (D3, D4). Es bien sabido que las bases débiles, apróticas, no nucleofílicas son preferidas con el fin de evitar la formación de amidas, por ejemplo dimetilaminopiridina (D1), NMM (D3), piridina (D3, D4) o trietilamina (D5). Por lo tanto, en ausencia de un efecto inesperado específico, la presente materia de las reivindicaciones 1 - 11 carece de nivel inventivo.

Por favor note que D2, en la página 7, 4º párrafo, ya dice que "...grupo acetal será resistente a los ácidos orgánicos bajo las condiciones de reacción utilizadas..." y por lo tanto no se puede asignar un efecto sorpresivo a la estabilidad de los acetales presentes bajo condiciones ácidas.

4 Aplicabilidad Industrial (Artículo 33(4) del PCT)

La materia de las presentes reivindicaciones 1 - 11 cumple con los requerimientos del Artículo 33(4) del PCT.

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 that Authority may be indicated by the applicant on the line below:

IPEA/EPN

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 IPEA		Date of receipt of DEMAND	
Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 20916WO	
International application No. PCT/NL03/00435	International filing date (day/month/year) 12 June 2003 (12.06.03)	(Earliest) Priority date (day/month/year) 17 June 2002 (17.06.02)	
Title of invention PROCESS FOR THE PREPARATION OF AN ESTER.			
Box No. II APPLICANT(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.) DSM IP Assets B.V. Het Overloon 1 6411 TE Heerlen the Netherlands		Telephone No.	
		Facsimile No.	
		Teleprinter No.	
		Applicant's registration No. with the Office	
State (that is, country) of nationality: NL		State (that is, country) of residence: NL	
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.) BAKEL VAN, Hermanus Carolus Catharina Karel Barbarastraat 10 5988 BC Helden the Netherlands			
State (that is, country) of nationality: NL		State (that is, country) of residence: NL	
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.) CALLANT, Dominique Monique Charles De Huttestraat 93 B-3530 Houthalen Belgium			
State (that is, country) of nationality: BE		State (that is, country) of residence: BE	
☒ Further applicants are indicated on a continuation sheet.			

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes 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.)

KOOISTRA, Jacob Hermanus Mattheus Hero
Gaspeldoornstraat 32
5925 BA Venlo
the Netherlands

State (that is, country) of nationality: NL

State (that is, country) of residence: NL

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.)

MAAS, Peter Johannes Dominicus
Geleenstraat 70
6155 ND Puth
the Netherlands

State (that is, country) of nationality: NL

State (that is, country) of residence: NL

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:

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 CORRESPONDENCEThe 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.)HERMANS, Edith Elisabeth Hermine
DSM Intellectual Property
Office Geleen
P.O. Box 9
6160 MA Geleen (NL)

Telephone No.

(+31)46-4767324

Facsimile No.

(+31)46-4761830

Teleprinter No.

Applicant'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 filed

the description

☐ as originally filed☐ as amended under Article 34

the claims

☐ as originally filed☐ as amended under Article 19 (together with any accompanying statement)☐ as amended under Article 34

the 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:☐ 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:

PATENT COOPERATION TREATY

PCT/NL2003/000435

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PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

From the INTERNATIONAL BUREAU

To:

ASTRAZENECA
R & D Headquarters
Global Intellectual Property,
Patents
S-151 85 Sodertalje
Sweden

Date of mailing (day/month/year)

07 January 2004 (07.01.2004)

Applicant's or agent's file reference

20916WO

IMPORTANT NOTIFICATION

International application No.

PCT/NL2003/000435

International filing date (day/month/year)

12 June 2003 (12.06.2003)

1. The following indications appeared on record concerning:

☐ the applicant

☐ the inventor

☒ the agent

☐ the common representative

Name and Address

HERMANS, Edith, Elisabeth, Hermine
DSM Patents & Trademarks
Office Geleen
P.O. Box 9
NL-6160 MA Geleen
Netherlands

State of Nationality

State of Residence

Telephone No.

31 46 4767324

Facsimile No.

31 46 4761830

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person

☐ the name

☐ the address

☐ the nationality

☐ the residence

Name and Address

ASTRAZENECA
R & D Headquarters
Global Intellectual Property,
Patents
S-151 85 Sodertalje
Sweden

State of Nationality

State of Residence

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

Please submit new Powers of Attorney in your favour from all applicants and furnish your file reference and telephone and fax numbers.

4. A copy of this notification has been sent to:

☒ the receiving Office

☐ the International Searching Authority

☒ the International Preliminary Examining Authority

☐ the designated Offices concerned

☒ the elected Offices concerned

☒ other: FORMER AGENT

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 338.89.65

Authorized officer

Nicole MILLIET

Telephone No. (41-22) 338 9066

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purpose 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 (<i>specify</i>) | : | sheets |

For International Preliminary
Examining Authority use only

received

not received

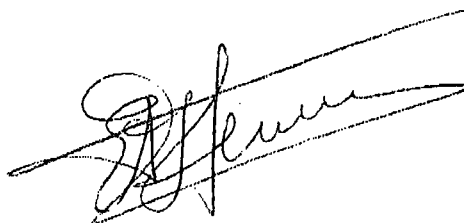
☐☐☐☐☐☐☐☐☐☐☐☐

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. ☐ tables in computer readable form related to sequence listings |
| 4. ☐ copy of general power of attorney;
reference number, if any: | 8. ☒ other (<i>specify</i>): request for detailed examination |

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).



E.E.H. Hermans

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 80.5. | |
| 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 82. | |

For International Bureau use only

Demand received from IPEA on:

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) 20916WO

Box No. I TITLE OF INVENTION
PROCESS FOR THE PREPARATION OF AN ESTER

Box No. II APPLICANT ☐ This person is also inventor

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.)

DSM IP Assets B.V.
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the Netherlands

Telephone No.

Facsimile No.

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality: NL

State (that is, country) of residence: NL

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) AND/OR (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.)

BAKEL VAN, Hermanus Carolus Catharina Karel
Barbarastraat 10
5988 BC Helden
the Netherlands

This person is:

☐

applicant only

☒

applicant and inventor

☐

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

Applicant's registration No. with the Office

State (that is, country) of nationality: NL

State (that is, country) of residence: NL

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.)

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Teleprinter No.

Applicant'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..

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S) <i>If none of the following sub-boxes is used, this sheet should not be included in the request</i>	
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.) CALLANT, Dominique Monique Charles De Huttestraat 93 B-3530 Houthalen Belgium	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality: BE	State (that is, country) of residence: BE
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	
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.) KOOISTRA, Jacob Hermanus Mattheus Hero Gaspeldoornstraat 32 5925 BA Venlo the Netherlands	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality: NL	State (that is, country) of residence: NL
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	
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.) MAAS, Peter Johannes Dominicus Geleenstraat 70 6155 ND Puth the Netherlands	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality: NL	State (that is, country) of residence: NL
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	
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 <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality: NL	State (that is, country) of residence: NL
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.	

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Box No.V	DESIGNATION OF STATES	Mark the applicable check-boxes below; at least one must be marked.
The following designations are hereby made under Rule 4.9(a):		
Regional Patent		
☒ AP	ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line).....	
☒ 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, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech, DE Germany, DK Denmark, EE Estonia, 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, SK Slovakia, 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, GQ Equatorial 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	☒ GM Gambia	☒ NZ New Zealand
☒ AG Antigua and Barbuda	☒ HR Croatia	☒ OM Oman.....
☒ AL Albania	☒ HU Hungary	☒ PH Philippines
☒ AM Armenia	☒ ID Indonesia	☒ PL Poland
☒ AT Austria	☒ IL Israel	☒ PT Portugal
☒ AU Australia	☒ IN India	☒ RO Romania
☒ AZ Azerbaijan	☒ IS Iceland	☒ RU Russian Federation
☒ BA Bosnia and Herzegovina	☒ JP Japan	☒ SD Sudan
☒ BB Barbados	☒ KE Kenya	☒ SE Sweden
☒ BG Bulgaria	☒ KG Kyrgyzstan	☒ SG Singapore
☒ BR Brazil	☒ KP Democratic People's Republic of Korea	☒ SI Slovenia
☒ BY Belarus	☒ KR Republic of Korea	☒ SK Slovakia
☒ BZ Belize	☒ KZ Kazakhstan	☒ SL Sierra Leone
☒ CA Canada	☒ LC Saint Lucia	☒ TJ Tajikistan
☒ CH & LI Switzerland and Liechtenstein	☒ LK Sri Lanka	☒ TM Turkmenistan
☒ CN China	☒ LR Liberia	☒ TN Tunisia.....
☒ CO Colombia	☒ LS Lesotho	☒ TR Turkey
☒ CR Costa Rica	☒ LT Lithuania	☒ TT Trinidad and Tobago
☒ CU Cuba	☒ LU Luxembourg	☒ TZ United Republic of Tanzania
☒ CZ Czech Republic	☒ LV Latvia	☒ UA Ukraine
☒ DE Germany	☒ MA Morocco	☒ UG Uganda
☒ DK Denmark	☒ MD Republic of Moldova	☒ US United States of America
☒ DM Dominica	☒ MG Madagascar	☒ UZ Uzbekistan
☒ DZ Algeria	☒ MK The former Yugoslav Republic of Macedonia	☒ VN Viet Nam
☒ EC Ecuador	☒ MN Mongolia	☒ YU Serbia and Montenegro
☒ EE Estonia	☒ MW Malawi	☒ ZA South Africa
☒ ES Spain	☒ MX Mexico	☒ ZM Zambia.....
☒ FI Finland	☒ MZ Mozambique	☒ ZW Zimbabwe
☒ GB United Kingdom	☒ NO Norway	
☒ GD Grenada		
☒ GE Georgia		
☒ GH Ghana		
Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:		
☒ VC Saint Vincent & Grenadines	☒ NI Nicaragua	☐
☒ SC Seychelles	☐	☐
Precautionary 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 15 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.)		

45

Hf

Box No. VI PRIORITY CLAIM				
The priority of the following earlier application(s) is hereby claimed:				
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	International application: receiving Office
item (1) 17 June 2002 (17.06.2002)	02100715.8		EP	
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

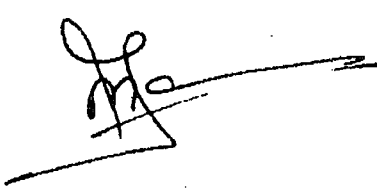
The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items
 ☐ item (1)
 ☐ item (2)
 ☐ item (3)
 ☐ item (4)
 ☐ item (5)
 ☐ other, see Supplemental box

*Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):

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 /		
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) 17-06-2002	Number 02100715.8	Country (or regional Office) Europe

Box No. VIII DECLARATIONS		Number of declarations
☐	Box No. VIII (i) Declaration as to the identity of the inventor :	
☐	Box No. VIII (ii) Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent :	
☐	Box No. VIII (iii) Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application :	
☐	Box No. VIII (iv) Declaration of inventorship (only for the purposes of the designation of the United States of America) :	
☐	Box No. VIII (v) Declaration as to non-prejudicial disclosures or exceptions to lack of novelty :	

Box No. IX CHECK LIST; LANGUAGE OF FILING																																					
This international application contains: (a) the following number of sheets in paper form: <table><tr><td>request (including declaration sheets)</td><td>: 5</td></tr><tr><td>description (excluding sequence listing part)</td><td>: 5</td></tr><tr><td>claims</td><td>: 2</td></tr><tr><td>abstract</td><td>: 1</td></tr><tr><td>drawings</td><td>:</td></tr></table> Sub-total number of sheets : 13 Sequence listing part of description (<i>actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below</i>) : Total number of sheets : 13 (b) sequence listing part of description filed in computer readable form (i) ☐ only (under Section 801(a)(i)) (ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii)) Type and number of carriers (diskette, CD-ROM, CR-R or other) on which the Sequence listing part is contained (additional copies to be indicated under item 9(ii), in right column) :	request (including declaration sheets)	: 5	description (excluding sequence listing part)	: 5	claims	: 2	abstract	: 1	drawings	:	This international application is accompanied by the following item(s) (<i>mark the applicable check-boxes below and indicate in right column the number of each item</i>): <table><tr><td>1. ☒ fee calculation sheet</td><td>: 1</td></tr><tr><td>2. ☐ original separate power of attorney</td><td>:</td></tr><tr><td>3. ☐ original general power of attorney</td><td>:</td></tr><tr><td>4. ☒ copy of the general power of attorney; reference number, if any:</td><td>: 1*</td></tr><tr><td>5. ☐ statement explaining lack of signature</td><td>:</td></tr><tr><td>6. ☒ priority document(s) identified in Box No. VI as item(s): 1</td><td>: 1</td></tr><tr><td>7. ☐ translation of international application into (language):</td><td>:</td></tr><tr><td>8. ☐ separate indications concerning deposited microorganism or other biological material</td><td>:</td></tr><tr><td>9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CR-R or other))</td><td>:</td></tr><tr><td> (i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)</td><td>:</td></tr><tr><td> (ii) ☐ (<i>only where check-box (b)(i) or (b)(ii) is marked in left column</i>) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter</td><td>:</td></tr><tr><td> (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column</td><td>:</td></tr><tr><td>10. ☐ other (<i>specify</i>):</td><td>:</td></tr></table>	1. ☒ fee calculation sheet	: 1	2. ☐ original separate power of attorney	:	3. ☐ original general power of attorney	:	4. ☒ copy of the general power of attorney; reference number, if any:	: 1*	5. ☐ statement explaining lack of signature	:	6. ☒ priority document(s) identified in Box No. VI as item(s): 1	: 1	7. ☐ translation of international application into (language):	:	8. ☐ separate indications concerning deposited microorganism or other biological material	:	9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CR-R or other))	:	(i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application)	:	(ii) ☐ (<i>only where check-box (b)(i) or (b)(ii) is marked in left column</i>) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter	:	(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	:	10. ☐ other (<i>specify</i>):	:
request (including declaration sheets)	: 5																																				
description (excluding sequence listing part)	: 5																																				
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10. ☐ other (<i>specify</i>):	:																																				
Figure of the drawings which should accompany the abstract:	Language of filing of the International application: English																																				
Box No. IX 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 request).																																					
 M.S.N. Jacobs																																					

For receiving Office use only	
1. Date of actual receipt of the purported International application:	2. Drawings: ☐ received: ☐ not received:
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 Corrections under PCT Article 11(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:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET
Annex to the Request

For receiving Office use only

Applicant's or agent's file reference: 20916WO Applicant: DSM N.V. CALCULATION OF PRESCRIBED FEES 1. TRANSMITTAL FEE 50,- T 2. SEARCH FEE 945,- S International search to be carried out by (If two or more International Searching Authorities are competent in relation to the international application, indicate the name of the Authority which is chosen to carry out the international search.) 3. INTERNATIONAL FEE Basic Fee Where item (b) of Box No. IX applies, enter Sub-total number of sheets 21 Where item (b) of Box No. IX does not apply, enter Total number of sheets b₁ first 30 sheets 444,- b₁ b₂ X x 10,- = b₂ number of sheets in excess of 30 fee per sheet additional component (only if sequence listing part of description is filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)): b₃ 400 x = b₃ fee per sheet 444,- B Add amounts entered at b₁, b₂ and b₃ and enter total at B Designation Fees The international application contains 92 designations. 5 x 96,- = D number of designation fees payable (maximum 5) amount of designation fee 924,- I Add amounts entered at B and D and enter total at I (Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.) P 4. FEE FOR PRIORITY DOCUMENT (if applicable) EUR 1.919,- 5. TOTAL FEES PAYABLE TOTAL Add amounts entered at T, S, I and P, and enter total in the TOTAL box	International application No. Date stamp of the receiving Office								
☐ The designation fees are not paid at this time.									
MODE OF PAYMENT <table style="width: 100%;"><tr><td>☒ authorization to charge deposit account (see below)</td><td>☐ postal money order</td><td>☐ cash</td><td>☐ coupons</td></tr><tr><td>☐ cheque</td><td>☐ bank draft</td><td>☐ revenue stamps</td><td>☐ other (specify):</td></tr></table>		☒ authorization to charge deposit account (see below)	☐ postal money order	☐ cash	☐ coupons	☐ cheque	☐ bank draft	☐ revenue stamps	☐ other (specify):
☒ authorization to charge deposit account (see below)	☐ postal money order	☐ cash	☐ coupons						
☐ cheque	☐ bank draft	☐ revenue stamps	☐ other (specify):						
AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT (this mode of payment may not be available at all receiving Offices) <table style="width: 100%;"><tr><td>☒ Authorization to charge the total fees indicated above.</td><td>Receiving Office: RO / NL</td></tr><tr><td>☒ (This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.</td><td>Deposit Account No.: 1500</td></tr><tr><td>☒ Authorization to charge the fee for priority document.</td><td>Date: 12 June 2003</td></tr><tr><td></td><td>Name: M.S.N. Jacobs</td></tr></table> Signature:		☒ Authorization to charge the total fees indicated above.	Receiving Office: RO / NL	☒ (This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	Deposit Account No.: 1500	☒ Authorization to charge the fee for priority document.	Date: 12 June 2003		Name: M.S.N. Jacobs
☒ Authorization to charge the total fees indicated above.	Receiving Office: RO / NL								
☒ (This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit) Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	Deposit Account No.: 1500								
☒ Authorization to charge the fee for priority document.	Date: 12 June 2003								
	Name: M.S.N. Jacobs								

Brigard & Castro

BOGOTA - COLOMBIA

PODER

POWER FATT RNEY

Yo (nosotros)

I (We) ASTRAZENECA UK LIMITED

domicillado(s) en

domiciled in 15 Stanhope Gate, London W1K 1LN
England

Nombro(amos) a: RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S.

Hereby appoint RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S.

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 enseñanzas, registros de derechos de autor y contratos sobre los mismos, obtención de certificados 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 clases; 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 o 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.

of 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 obtainers of vegetables 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.

A este efecto, lo(s) facuto(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 desistír 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 todos los pasos necesarios al efecto indicado y tomar todas las medidas que creyeren conducentes al resguardo de mis (nuestros) intereses, con todas las demás facultades legales necesarias.

To that effect they are 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 kind 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) interest(s) with all the other necessary legal powers.

Este poder comprende la facultad de ratificar o confirmar en mi (nuestro) nombre lo actuado así como la facultad de desistír, transigir, comprometer, y la de sustituirlo en todo o en parte y revocar sustituciones. Asimismo nombro(amos) a: RAMIRO CASTRO DUQUE y/o JUAN PABLO CADENA SARMIENTO y/o BEATRIZ JARAMILLO S. domiciliado(s) en la Carrera 7 No. 18-58 Piso 9, mis (nuestros) apoderados en Colombia, con facultades para recibir notificaciones y designar apoderados judiciales o extrajudiciales.

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. At the same time I (We) hereby appoint RAMIRO CASTRO DUQUE and/or JUAN PABLO CADENA SARMIENTO and/or BEATRIZ JARAMILLO S. domiciled in Carrera 7 No. 18-58 Piso 9, my (our) attorney(s) in fact, with full powers to receive notifications and to designate judicial or extrajudicial attorneys.

Otorgado y firmado en

Granted and signed in Bogotá, Colombia, this 10th day of March 2004

hoy de de 200_

Firma

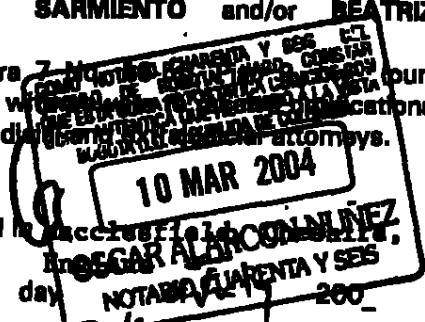
Signature

Nombre

Name KEVIN BELL

Cargo

Title Director, IP Services



120816

CERTIFICADO 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

Sociedad legalmente constituida para un período 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 pie 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 es(son) la(s) persona(s) firmante(s) del documento que precede y quien(es) declara(n) que otorgan el mismo para los fines y propósitos que en él se expresan.

Notario Público (sello)

LEGALIZACION POR APOSTILLA ES REQUERIDA.

NOTARIAL CERTIFICATE (CORPORATION)

On this 18th day of July 2003 of
personally appeared before me

KEVIN BILL
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

of ATTORNEY of
ASTRAZENECA UK LIMITED

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 England
under date of 12th July 2003

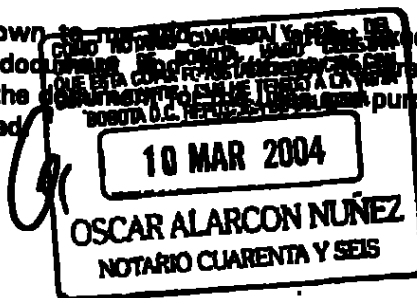
and that he (she) is duly authorized to grant power of attorney is its Representative

Notary Public (Seal)

**NOTARIAL CERTIFICATE
NATURAL PERSON**

On this day of of
personally appeared before me

who is(are) known to me and known to me to be the person(s) who executed the foregoing document and who declared he (they) grant(s) the document for the purposes therein expressed



Notary Public (Seal)

LEGALIZATION BY APOSTILLE IS REQUIRED.

ORATION)

APOSTILLE

(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by J B Hodgson
a été signé par

3. Acting in the capacity of Notary Public
agissant en qualité de

4. Bears the seal/stamp of The Said Notary Public
est revêtu du sceau/sigilure de

5. at London/Londres
Certified/Attesté
6. the/le 13 February 2004

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

8. Number/num No **G346692**

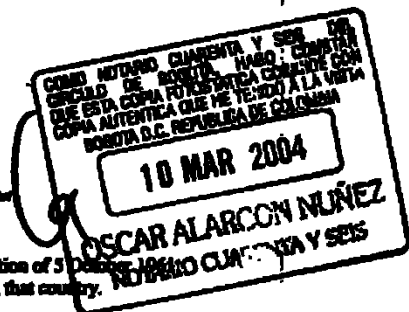
9. Stamp:
timbre:

10. Signature: W. Glass



For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
it should be presented to the consular section of the mission representing that country.





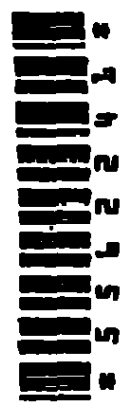
GAVIRI A

5/30

ORGANIZACION ELECTORAL
REGISTRADURIA NACIONAL DEL ESTADO CIVIL

REGISTRO CIVIL DE DEFUNCION

Indicativo
Serial 5562241



Datos de la oficina de registro									
Clase de oficina:	Registraduría	Notaría	☒	Consular	Corregimiento	Ins. de Policía	Código	9795	
País - Departamento - Municipio - Corregimiento o Inspección de Policía									
COLOMBIA CUNDINAMARCA BOGOTA D.C. NOTARIA 32.									

Datos del inscrito	
Apellidos y nombres completos	
CASTRO DUQUE RAMIRO	
Documento de identificación (Clase y número)	Sexo (en Letras)
C.C.No. 170322 DE BOGOTA	MASCULINO

Datos de la defunción			
Lugar de la Defunción País - Departamento - Municipio - Corregimiento o Inspección de Policía			
COLOMBIA CUNDINAMARCA BOGOTA D.C.			
Fecha de la defunción		Hora	Número de certificado de defunción
Año 2004	Mes 10	Día 30 04:10 PM	A- 2094375.
Presunción de muerte		Fecha de la sentencia	
Según que probare la sentencia		Año Mes Día	
Documento presentado		Nombre y cargo del testamento	
Autenticación judicial	Certificado FMI-80 ☒	ANDRES DIAZ CAMPOS.- R. M. No. 79982662	

Datos del denunciante	
Apellidos y nombres completos	
EDGAR DAVID REGINO II.	
Documento de identificación (Clase y número)	Firma
C.C.N. 15.030.154 DE LORICA/ CORDOBA	

Primer testigo	
Apellidos y nombres completos	
Documento de identificación (Clase y número)	
Firma	

Segundo testigo	
Apellidos y nombres completos	
Documento de identificación (Clase y número)	
Firma	

Fecha de inscripción		Nombre y firma del testamento que se inscribe	
Año 2004	Mes 10	Día 02	BLANCA CHUPELEO RESTREPO NOTARIA

PADRES: ALFONSO CASTRO		ESPACIO PARA NOTAS	
MERCEDES DUQUE.			

ORIGINAL PARA LA OFICINA DE REGISTRO

NOTARIA 32

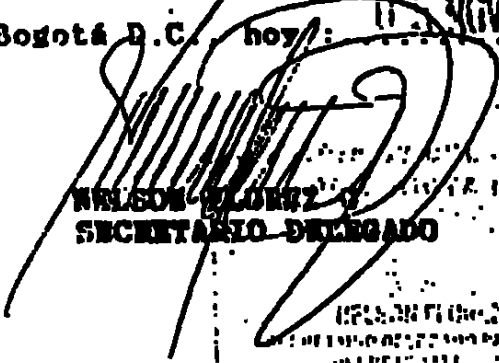
DEL CIRCULO DE SANTA FE DE BOGOTA, D.C.

Germán Eleazar Moreno L.
Notario

COMO SECRETARIO DELEGADO DE LA NOTARIA TREINTA Y DOS (32) DEL
CIRCULO DE BOGOTA

CERTIFICO, QUE:

La presente acta es fiel copia del original tomada del registr
civil de defunciones serial indicativo número: 5562241.....
que expido en la ciudad de Bogotá D.C. hoy: 11 de mayo de 2004.....


NELSON ALVARADO
SECRETARIO DELEGADO

BOGOTA D.C. 11 DE MAYO DE 2004

51

82

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL
TRAMITE

PATENTE DE INVENCIÓN

MODELO DE UTILIDAD

- | | USUARIO | PROCESADOR |
|--|---------|------------|
| - Indicación de que se solicita la concesión de una patente. | () | () |
| - Datos de identificación del solicitante o de la persona que 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 o 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:



SUPERINDUSTRIA Y COMERCIO

Radicación : 04129311 00000000

Folios: 51

Fecha: Fecha (AMD): 2004-12-20 16:39:52

Trámite : 011 PCT-PATENT 379 FASE INCI 411 PRESENTAC

Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

2020
Bogotá D C

Doctor(a)
JUAN PABLO CADENA SARMIENTO
Apoderado(a)
ASTRAZENECA UK LIMITED

Oficio N° **11916**

ASUNTO:

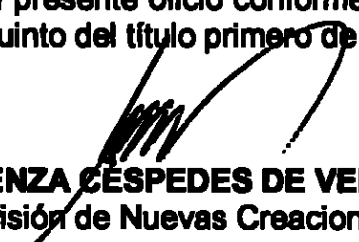
Radicación N°	04-129311
Solicitud internacional	PCTNL03/00435
Fecha inicio fase nacional	17/01/2005
Trámite	011
Evento	379
Actuación	430
Folios	001

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 copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k Decisión 486).

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.


ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha,
21 ENE 2005

202044

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
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Sede CAN: Tr. 40A No. 38-50 3153265 al 69
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Bogotá D.C. - Colombia