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A.A. 6349
Santa Fe de Bogotá, D.C., COLOMBIA

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 00049356 00000002 Folios: 44
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Tramite : 002 PATENTES D 1 REGISTRO/ 329 COMPLEMEN
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Señora

Jefe de la División de Nuevas Creaciones

Superintendencia de Industria y Comercio

Ministerio de Desarrollo Económico

E. S. D.

Ref.: Expediente No. **00.049.356**

Solicitud de Patente de Invención titulada : **"SINTESIS MEJORADA
DEL LIGANDO MACROCICLICO DE TETRAMIDO A PARTIR DE UN
NUEVO DIAMIDODIOL"**.

Solicitante: **THE CLOROX COMPANY**

Yo, **MARGARITA CASTELLANOS ABONDANO**, mayor de edad,
identificada y domiciliada como aparece al pié de mi firma, atentamente me
permito presentar a usted la copia certificada del documento de Prioridad
Americano No. **09/347435** de **Julio 2 de 1.999**, junto con la traducción de
las reivindicaciones.

En consecuencia atentamente solicito a Ud. se anexe dicho documento
al expediente correspondiente a esta solicitud de Patente de Invención

Del Señor Jefe,


Margarita Castellanos Abondano
C.C. No. **39.779.654** de Usaquén
T.P.A. No. **70819** del Consejo Sup. de la Judicatura
Carrera 9ª. No. 93 - 09 - Santa Fe de Bogotá
Teléfonos: 610 74 80 y 610 74 60

Santa Fe de Bogotá, D.C.,
xgt/4752

04 SET. 2000

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United States of America



DEPARTMENT OF STATE

*To all to whom these presents shall come, Greetings:*

I Certify That the document hereunto annexed is under the Seal of the Patent and Trademark Office, Department of Commerce, United States of America, and that such Seal is entitled to full faith and credit.*

In testimony whereof, I, Frank E. Loy, Acting Secretary of State, have hereunto caused the seal of the Department of State to be affixed and my name subscribed by the Assistant Authentication Officer, of the said Department, at the city of Washington, in the District of Columbia, this fifth day of June, 2000.

Acting Secretary of State

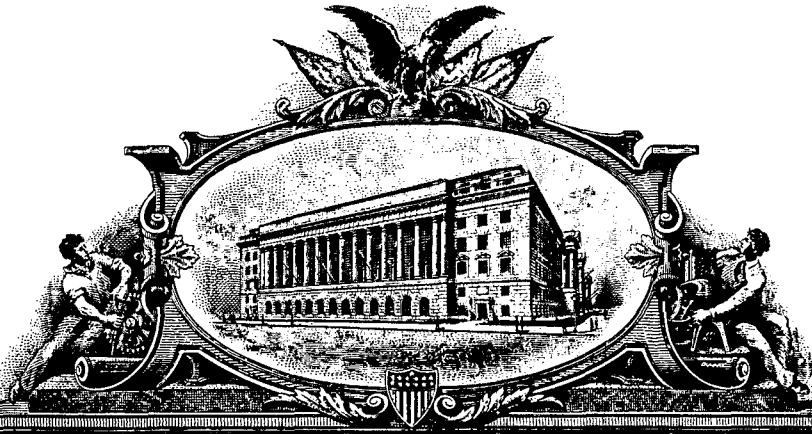
By

Assistant Authentication Officer,
Department of State

Issued pursuant to CHXIV, State of
Sept. 15, 1789, 1 Stat. 68-69; 22
USC 2657; 22USC 2651a; 5 USC
301; 28 USE 1733 et. seq.; 8 USC
1443(f); RULE 44 Federal Rules of
Civil Procedure.

***For the contents of the annexed document, the Department assumes no responsibility**

This certificate is not valid if it is removed or altered in any way whatsoever



THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

May 04, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 09/347,435 ✓

FILING DATE: July 02, 1999



**By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS**

W. Montgomery
W. MONTGOMERY
Certifying Officer



Preliminary Classification:

Proposed Class:

Subclass:

NOTE: "All applicants are requested to include a preliminary classification on newly filed patent applications. The preliminary classification, preferably class and subclass designations, should be identified in the upper right-hand corner of the letter of transmittal accompanying the application papers, for example 'Proposed Class 2, subclass 129.'" M.P.E.P. § 601, 7th ed.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Box Patent Application
Assistant Commissioner for Patents
Washington, D.C. 20231

NEW APPLICATION TRANSMITTAL

Transmitted herewith for filing is the patent application of
Inventor(s): James E. Deline and Michael M. Ott

WARNING: 37 C.F.R. § 1.41(a)(1) points out:

"(a) A patent is applied for in the name or names of the actual inventor or inventors.

"(1) The inventorship of a nonprovisional application is that inventorship set forth in the oath or declaration as prescribed by § 1.63, except as provided for in § 1.53(d)(4) and § 1.63(d). If an oath or declaration as prescribed by § 1.63 is not filed during the pendency of a nonprovisional application, the inventorship is that inventorship set forth in the application papers filed pursuant to § 1.53(b), unless a petition under this paragraph accompanied by the fee set forth in § 1.17(i) is filed supplying or changing the name or names of the inventor or inventors."

For (title): IMPROVED SYNTHESIS OF A TETRAAMIDO MACROCYCLE LIGAND FROM A NOVEL DIAMIDODIOL

CERTIFICATION UNDER 37 C.F.R. § 1.10*

(Express Mail label number is mandatory.)

(Express Mail certification is optional.)

I hereby certify that this New Application Transmittal and the documents referred to as attached therein are being deposited with the United States Postal Service on this date July 2, 1999, in an envelope as "Express Mail Post Office to Addressee," mailing Label Number _____, addressed to the: Assistant Commissioner for Patents, Washington, D.C. 20231.

Mark E. Baze

(type or print name of person mailing paper)

Mark Baze

Signature of person mailing paper

WARNING: Certificate of mailing (first class) or facsimile transmission procedures of 37 C.F.R. § 1.8 cannot be used to obtain a date of mailing or transmission for this correspondence.

***WARNING:** Each paper or fee filed by "Express Mail" must have the number of the "Express Mail" mailing label placed thereon prior to mailing. 37 C.F.R. § 1.10(b).

"Since the filing of correspondence under § 1.10 without the Express Mail mailing label thereon is an oversight that can be avoided by the exercise of reasonable care, requests for waiver of this requirement will not be granted on petition." Notice of Oct. 24, 1996, 60 Fed. Reg. 56,439, at 56,442.

(New Application Transmittal [4-1]—page 1 of 11)

1. Type of Application

This new application is for a(n)

(check one applicable item below)

- ☒ Original (nonprovisional)
☐ Design
☐ Plant

WARNING: Do not use this transmittal for a completion in the U.S. of an International Application under 35 U.S.C. § 371(c)(4), unless the International Application is being filed as a divisional, continuation or continuation-in-part application.

WARNING: Do not use this transmittal for the filing of a provisional application.

NOTE: If one of the following 3 items apply, then complete and attach **ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF A PRIOR U.S. APPLICATION CLAIMED** and a **NOTIFICATION IN PARENT APPLICATION OF THE FILING OF THIS CONTINUATION APPLICATION**.

- ☐ Divisional.
☐ Continuation.
☐ Continuation-in-part (C-I-P).

2. Benefit of Prior U.S. Application(s) (35 U.S.C. §§ 119(e), 120, or 121)

NOTE: A nonprovisional application may claim an invention disclosed in one or more prior filed copending nonprovisional applications or copending international applications designating the United States of America. In order for a nonprovisional application to claim the benefit of a prior filed copending nonprovisional application or copending international application designating the United States of America, each prior application must name as an inventor at least one inventor named in the later filed nonprovisional application and disclose the named inventor's invention claimed in at least one claim of the later filed nonprovisional application in the manner provided by the first paragraph of 35 U.S.C. § 112. Each prior application must also be:

(i) An international application entitled to a filing date in accordance with PCT Article 11 and designating the United States of America; or

(ii) Complete as set forth in § 1.51(b); or

(iii) Entitled to a filing date as set forth in § 1.53(b) or § 1.53(d) and include the basic filing fee set forth in § 1.16; or

(iv) Entitled to a filing date as set forth in § 1.53(b) and have paid therein the processing and retention fee set forth in § 1.21(f) within the time period set forth in § 1.53(f).

37 C.F.R. § 1.78(a)(1).

NOTE: If the new application being transmitted is a divisional, continuation or a continuation-in-part of a parent case, or where the parent case is an International Application which designated the U.S., or benefit of a prior provisional application is claimed, then check the following item and complete and attach **ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED**.

WARNING: If an application claims the benefit of the filing date of an earlier filed application under 35 U.S.C. §§ 120, 121 or 365(c), the 20-year term of that application will be based upon the filing date of the earliest U.S. application that the application makes reference to under 35 U.S.C. §§ 120, 121 or 365(c). (35 U.S.C. § 154(a)(2) does not take into account, for the determination of the patent term, any application on which priority is claimed under 35 U.S.C. §§ 119, 365(a) or 365(b).) For a c-i-p application, applicant should review whether any claim in the patent that will issue is supported by an earlier application and, if not, the applicant should consider canceling the reference to the earlier filed application. The term of a patent is not based on a claim-by-claim approach. See Notice of April 14, 1995, 60 Fed. Reg. 20,195, at 20,205.

(New Application Transmittal [4-1]—page 2 of 11)

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WARNING: When the last day of pendency of a provisional application falls on a Saturday, Sunday, or Federal holiday within the District of Columbia, any nonprovisional application claiming benefit of the provisional application must be filed prior to the Saturday, Sunday, or Federal holiday within the District of Columbia. See 37 C.F.R. § 1.78(a)(3).

- ☐ The new application being transmitted claims the benefit of prior U.S. application(s). Enclosed are ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.

3. Papers Enclosed

- A.** Required for filing date under 37 C.F.R. § 1.53(b) (Regular) or 37 C.F.R. § 1.153 (Design) Application

13 Pages of specification
6
 Pages of claims
2 Sheets of drawing

WARNING: DO NOT submit original drawings. A high quality copy of the drawings should be supplied when filing a patent application. The drawings that are submitted to the Office must be on strong, white, smooth, and non-shiny paper and meet the standards according to § 1.84. If corrections to the drawings are necessary, they should be made to the original drawing and a high-quality copy of the corrected original drawing then submitted to the Office. Only one copy is required or desired. For comments on proposed then-new 37 C.F.R. § 1.84, see Notice of March 9, 1988 (1990 O.G. 57-62).

NOTE: "Identifying Indicia, if provided, should include the application number or the title of the invention, inventor's name, docket number (if any), and the name and telephone number of a person to call if the Office is unable to match the drawings to the proper application. This information should be placed on the back of each sheet of drawing a minimum distance of 1.5 cm. (5/8 inch) down from the top of the page . . ." 37 C.F.R. § 1.84(c).

(complete the following, if applicable)

- ☐ The enclosed drawing(s) are photograph(s), and there is also attached a "PETITION TO ACCEPT PHOTOGRAPH(S) AS DRAWING(S)." 37 C.F.R. § 1.84(b).

- ☐ formal
☒ informal

B. Other Papers Enclosed

2 Pages of declaration and power of attorney
1 Pages of abstract
 Other

4. Additional papers enclosed

- ☐ Amendment to claims
- ☐ Cancel in this applications claims _____ before calculating the filing fee. (At least one original independent claim must be retained for filing purposes.)
- ☐ Add the claims shown on the attached amendment. (Claims added have been numbered consecutively following the highest numbered original claims.)
- ☐ Preliminary Amendment
- ☐ Information Disclosure Statement (37 C.F.R. § 1.98)
- ☐ Form PTO-1449 (PTO/SB/08A and 08B)
- ☐ Citations

(New Application Transmittal [4-1]—page 3 of 11)

- 7
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- ☐ Declaration of Biological Deposit
 - ☐ Submission of "Sequence Listing," computer readable copy and/or amendment pertaining thereto for biotechnology invention containing nucleotide and/or amino acid sequence.
 - ☐ Authorization of Attorney(s) to Accept and Follow Instructions from Representative
 - ☐ Special Comments
 - ☐ Other

5. Declaration or oath (including power of attorney)

NOTE: A newly executed declaration is not required in a continuation or divisional application provided that the prior nonprovisional application contained a declaration as required, the application being filed is by all or fewer than all the inventors named in the prior application, there is no new matter in the application being filed, and a copy of the executed declaration filed in the prior application (showing the signature or an indication thereon that it was signed) is submitted. The copy must be accompanied by a statement requesting deletion of the names of person(s) who are not inventors of the application being filed. If the declaration in the prior application was filed under § 1.47, then a copy of that declaration must be filed accompanied by a copy of the decision granting § 1.47 status or, if a nonsigning person under § 1.47 has subsequently joined in a prior application, then a copy of the subsequently executed declaration must be filed. See 37 C.F.R. §§ 1.63(d)(1)-(3).

NOTE: A declaration filed to complete an application must be executed, identify the specification to which it is directed, identify each inventor by full name including family name and at least one given name, without abbreviation together with any other given name or initial, and the residence, post office address and country or citizenship of each inventor, and state whether the inventor is a sole or joint inventor. 37 C.F.R. § 1.63(a)(1)-(4).

- ☒ Enclosed

Executed by

(check all applicable boxes)

- ☒ inventor(s).
- ☐ legal representative of inventor(s).
37 C.F.R. §§ 1.42 or 1.43.
- ☐ joint inventor or person showing a proprietary interest on behalf of inventor who refused to sign or cannot be reached.
- ☐ This is the petition required by 37 C.F.R. § 1.47 and the statement required by 37 C.F.R. § 1.47 is also attached. See item 13 below for fee.

- ☐ Not Enclosed.

NOTE: Where the filing is a completion in the U.S. of an International Application or where the completion of the U.S. application contains subject matter in addition to the International Application, the application may be treated as a continuation or continuation-in-part, as the case may be, utilizing ADDED PAGE FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION CLAIMED.

- ☐ Application is made by a person authorized under 37 C.F.R. § 1.41(c) on behalf of all the above named inventor(s).

(The declaration or oath, along with the surcharge required by 37 C.F.R. § 1.16(e) can be filed subsequently).

- ☐ Showing that the filing is authorized.
(not required unless called into question. 37 C.F.R. § 1.41(d))

(New Application Transmittal [4-1]—page 4 of 11)

6. Inventorship Statement

WARNING: If the named inventors are each not the inventors of all the claims an explanation, including the ownership of the various claims at the time the last claimed invention was made, should be submitted.

The inventorship for all the claims in this application are:

☒ The same.

or

- ☐ Not the same. An explanation, including the ownership of the various claims at the time the last claimed invention was made,
- ☐ is submitted.
- ☐ will be submitted.

7. Language

NOTE: An application including a signed oath or declaration may be filed in a language other than English. An English translation of the non-English language application and the processing fee of \$130.00 required by 37 C.F.R. § 1.17(k) is required to be filed with the application, or within such time as may be set by the Office. 37 C.F.R. § 1.52(d).

☒ English

☐ Non-English

- ☐ The attached translation includes a statement that the translation is accurate. 37 C.F.R. § 1.52(d).

8. Assignment

☒ An assignment of the invention to The Clorox Company
Oakland, California

- ☐ is attached. A separate ☐ "COVER SHEET FOR ASSIGNMENT (DOCUMENT) ACCOMPANYING NEW PATENT APPLICATION" or ☐ FORM PTO 1595 is also attached.

☒ will follow.

NOTE: "If an assignment is submitted with a new application, send two separate letters—one for the application and one for the assignment." Notice of May 4, 1990 (1114 O.G. 77-78).

WARNING: A newly executed "CERTIFICATE UNDER 37 C.F.R. § 3.73(b)" must be filed when a continuation-in-part application is filed by an assignee. Notice of April 30, 1993, 1150 O.G. 62-64.

(New Application Transmittal [4-1]—page 5 of 11)

9. Certified Copy

Certified copy(ies) of application(s)

Country	Appln. No.	Filed
Country	Appln. No.	Filed
Country	Appln. No.	Filed

from which priority is claimed

- ☐ Is (are) attached.
☐ will follow.

NOTE: The foreign application forming the basis for the claim for priority must be referred to in the oath or declaration. 37 C.F.R. § 1.55(a) and 1.63.

NOTE: This item is for any foreign priority for which the application being filed directly relates. If any parent U.S. application or International Application from which this application claims benefit under 35 U.S.C. § 120 is itself entitled to priority from a prior foreign application, then complete item 18 on the ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED.

10. Fee Calculation (37 C.F.R. § 1.16)

A. ☒ Regular application

CLAIMS AS FILED			
Number filed	Number Extra	Rate	Basic Fee 37 C.F.R. § 1.16(a) \$760.00
Total			
Claims (37 C.F.R. § 1.16(c))	20 - 20 =	× \$ 18.00	.00
Independent			
Claims (37 C.F.R. § 1.16(b))	4 - 3 =	1 × \$ 78.00	78.00
Multiple dependent claim(s), if any (37 C.F.R. § 1.16(d))			
	0 +	\$260.00	.00

- ☐ Amendment cancelling extra claims is enclosed.
☐ Amendment deleting multiple-dependencies is enclosed.
☐ Fee for extra claims is not being paid at this time.

NOTE: If the fees for extra claims are not paid on filing they must be paid or the claims cancelled by amendment, prior to the expiration of the time period set for response by the Patent and Trademark Office in any notice of fee deficiency. 37 C.F.R. § 1.16(d).

Filing Fee Calculation \$838.00

B. ☐ Design application
(\$310.00—37 C.F.R. § 1.16(f))

Filing Fee Calculation \$

C. ☐ Plant application
(\$480.00—37 C.F.R. § 1.16(g))

Filing fee calculation \$

(New Application Transmittal [4-1]—page 6 of 11)

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11. Small Entity Statement(s)

- ☐ Statement(s) that this is a filing by a small entity under 37 C.F.R. § 1.9 and 1.27 is (are) attached.

WARNING: "Status as a small entity must be specifically established in each application or patent in which the status is available and desired. Status as a small entity in one application or patent does not affect any other application or patent, including applications or patents which are directly or indirectly dependent upon the application or patent in which the status has been established. The refiling of an application under § 1.53 as a continuation, division, or continuation-in-part (including a continued prosecution application under § 1.53(d)), or the filing of a reissue application requires a new determination as to continued entitlement to small entity status for the continuing or reissue application. A nonprovisional application claiming benefit under 35 U.S.C. § 119(e), 120, 121, or 365(c) of a prior application, or a reissue application may rely on a statement filed in the prior application or in the patent if the nonprovisional application or the reissue application includes a reference to the statement in the prior application or in the patent or includes a copy of the statement in the prior application or in the patent and status as a small entity is still proper and desired. The payment of the small entity basic statutory filing fee will be treated as such a reference for purposes of this section." 37 C.F.R. § 1.28(a)(2).

WARNING: "Small entity status must not be established when the person or persons signing the . . . statement can unequivocally make the required self-certification." M.P.E.P., § 509.03, 6th ed., rev. 2, July 1996 (emphasis added).

(complete the following, if applicable)

- ☐ Status as a small entity was claimed in prior application
_____ / _____, filed on _____, from which benefit
is being claimed for this application under:

35 U.S.C. § ☐ 119(e),
☐ 120,
☐ 121,
☐ 365(c),

and which status as a small entity is still proper and desired.

- ☐ A copy of the statement in the prior application is included.

Filing Fee Calculation (50% of A, B or C above)

\$ _____

NOTE: Any excess of the full fee paid will be refunded if small entity status is established and a refund request are filed within 2 months of the date of timely payment of a full fee. The two-month period is not extendable under § 1.136. 37 C.F.R. § 1.28(a).

12. Request for International-Type Search (37 C.F.R. § 1.104(d))

(complete, if applicable)

- ☐ Please prepare an international-type search report for this application at the time when national examination on the merits takes place.

13. Fee Payment Being Made at This Time

☐ Not Enclosed

☐ No filing fee is to be paid at this time.

(This and the surcharge required by 37 C.F.R. § 1.16(e) can be paid subsequently.)

☒ Enclosed

☒ Filing fee

\$ 838.00

☐ Recording assignment

(\$40.00; 37 C.F.R. § 1.21(h))

(See attached "COVER SHEET FOR
ASSIGNMENT ACCOMPANYING NEW
APPLICATION".)

\$ _____

☐ Petition fee for filing by other than all the
inventors or person on behalf of the inventor
where inventor refused to sign or cannot be
reached

(\$130.00; 37 C.F.R. §§ 1.47 and 1.17(i))

\$ _____

☐ For processing an application with a
specification in

a non-English language

(\$130.00; 37 C.F.R. §§ 1.52(d) and 1.17(k))

\$ _____

☐ Processing and retention fee

(\$130.00; 37 C.F.R. §§ 1.53(d) and 1.21(f))

\$ _____

☐ Fee for international-type search report

(\$40.00; 37 C.F.R. § 1.21(e))

\$ _____

NOTE: 37 C.F.R. § 1.21(f) establishes a fee for processing and retaining any application that is abandoned for failing to complete the application pursuant to 37 C.F.R. § 1.53(f) and this, as well as the changes to 37 C.F.R. §§ 1.53 and 1.78(a)(1), indicate that in order to obtain the benefit of a prior U.S. application, either the basic filing fee must be paid, or the processing and retention fee of § 1.21(f) must be paid, within 1 year from notification under § 53(f).

Total fees enclosed

\$ 838.00

14. Method of Payment of Fees

☐ Check in the amount of \$ _____

☒ Charge Account No. 03-2270 in the amount of
\$ 838.00

A duplicate of this transmittal is attached.

NOTE: Fees should be itemized in such a manner that it is clear for which purpose the fees are paid. 37 C.F.R. § 1.22(b).

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15. Authorization to Charge Additional Fees

WARNING: If no fees are to be paid on filing, the following items should not be completed.

WARNING: Accurately count claims, especially multiple dependent claims, to avoid unexpected high charges, if extra claim charges are authorized.

- ☒ The Commissioner is hereby authorized to charge the following additional fees by this paper and during the entire pendency of this application to Account No. _____

☒ 37 C.F.R. § 1.16(a), (f) or (g) (filing fees)

☒ 37 C.F.R. § 1.16(b), (c) and (d) (presentation of extra claims)

NOTE: Because additional fees for excess or multiple dependent claims not paid on filing or on later presentation must only be paid or these claims cancelled by amendment prior to the expiration of the time period set for response by the PTO in any notice of fee deficiency (37 C.F.R. § 1.16(d)), it might be best not to authorize the PTO to charge additional claim fees, except possibly when dealing with amendments after final action.

☒ 37 C.F.R. § 1.16(e) (surcharge for filing the basic filing fee and/or declaration on a date later than the filing date of the application)

☒ 37 C.F.R. § 1.17(a)(1)–(5) (extension fees pursuant to § 1.136(a)).

☒ 37 C.F.R. § 1.17 (application processing fees)

NOTE: ". . . A written request may be submitted in an application that is an authorization to treat any concurrent or future reply, requiring a petition for an extension of time under this paragraph for its timely submission, as incorporating a petition for extension of time for the appropriate length of time. An authorization to charge all required fees, fees under § 1.17, or all required extension of time fees will be treated as a constructive petition for an extension of time in any concurrent or future reply requiring a petition for an extension of time under this paragraph for its timely submission. Submission of the fee set forth in § 1.17(a) will also be treated as a constructive petition for an extension of time in any concurrent reply requiring a petition for an extension of time under this paragraph for its timely submission." 37 C.F.R. § 1.136(a)(3).

☒ 37 C.F.R. § 1.18 (issue fee at or before mailing of Notice of Allowance, pursuant to 37 C.F.R. § 1.311(b))

NOTE: Where an authorization to charge the issue fee to a deposit account has been filed before the mailing of a Notice of Allowance, the issue fee will be automatically charged to the deposit account at the time of mailing the notice of allowance. 37 C.F.R. § 1.311(b).

NOTE: 37 C.F.R. § 1.28(b) requires "Notification of any change in status resulting in loss of entitlement to small entity status must be filed in the application . . . prior to paying, or at the time of paying, . . . the issue fee. . . ." From the wording of 37 C.F.R. § 1.28(b), (a) notification of change of status must be made even if the fee is paid as "other than a small entity" and (b) no notification is required if the change is to another small entity.

(New Application Transmittal [4-1]—page 9 of 11)

16. Instructions as to Overpayment

NOTE: "... Amounts of twenty-five dollars or less will not be returned unless specifically requested within a reasonable time, nor will the payer be notified of such amounts; amounts over twenty-five dollars may be returned by check or, if requested, by credit to a deposit account." 37 C.F.R. § 1.26(a).

- ☒ Credit Account No. 03-2270
☐ Refund

Reg. No. 40,379

Tel. No. (510) 271-4982

Customer No.

251.98

Mark E. Baze
SIGNATURE OF PRACTITIONER

Mark E. Baze

(type or print name of attorney)

THE CLOROX COMPANY

P.O. Box 24305

P.O. Address

Oakland, California 94623

(New Application Transmittal [4-1]—page 10 of 11)

☐ **Incorporation by reference of added pages**

(check the following item if the application in this transmittal claims the benefit of prior U.S. application(s) (including an international application entering the U.S. stage as a continuation, divisional or C-I-P application) and complete and attach the ADDED PAGES FOR NEW APPLICATION TRANSMITTAL WHERE BENEFIT OF PRIOR U.S. APPLICATION(S) CLAIMED)

- ☐ Plus Added Pages for New Application Transmittal Where Benefit of Prior U.S. Application(s) Claimed

Number of pages added _____

- ☐ Plus Added Pages for Papers Referred to in Item 4 Above

Number of pages added _____

- ☐ Plus added pages deleting names of inventor(s) named in prior application(s) who is/are no longer inventor(s) of the subject matter claimed in this application.

Number of pages added _____

- ☐ Plus "Assignment Cover Letter Accompanying New Application"

Number of pages added _____

☒ **Statement Where No Further Pages Added**

(if no further pages form a part of this Transmittal, then end this Transmittal with this page and check the following item)

- ☒ This transmittal ends with this page.

15
58
56

**IMPROVED SYNTHESIS OF A TETRAAMIDO MACROCYCLE LIGAND
FROM A NOVEL DIAMIDODIOL**

Inventors: James E. Deline, Michael M. Ott

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FIELD OF THE INVENTION

The present invention relates to tetraamido macrocyclic ligands that form complexes with transition metals, and more particularly to the synthesis of a novel diamidiol that is used
10 as a substrate in an improved synthesis of macrocycles such as exemplified by 5,6-Benzo-3,8,11,13-tetraoxo-2,2,9,9-tetramethyl-12,12-diethyl-1,4,7,10-tetraazacyclotridecane, H₄

BACKGROUND OF THE INVENTION

The use of transition metal chelates as catalysts for bleaching agents is well known in
15 the art. For example, U.S. Pat. No. 4,119,557, issued to Postlethwaite, discloses the use of iron-polycarboxyamine complexes with hydrogen peroxide releasing substances to clean fabrics. Similarly, U.S. Pat. No. 5,244,594 (Favre et al.), U.S. Pat. No. 5,246,621 (Favre et al.), U.S. Pat. No. 5,194,416 (Jureller et al.), and U.S. Pat. No. 5,314,635 (Hage et al.) describe the use of manganese complexes of nitrogen- (or other heteroatom-) coordinated
20 macrocycles as catalysts for peroxy compounds.

The utility of compounds of this type has motivated researchers to develop new ligands that both stabilize the catalyst complex and that are able to withstand an oxidative environment. Promising ligands in this respect are the tetraamido macrocycles represented
25 by structure 10 shown in Fig. 1 which, when complexed with a transition metal such as iron, afford particularly good dye transfer inhibition capabilities.

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An azide-based synthesis of the macrocycle is described by Collins et al. in *J. Am. Chem. Soc.*, vol. 113, No. 22, page 8419 (1991). A problem with this synthesis is that it produces the tetraamido macrocycle in yields of only about 12% (starting from 1,2-phenylenediamine, as shown in the scheme at page 8422 of the article) and employs isolation techniques which cannot be adapted to large scale production. (Note: The identical synthesis is described by Erich S. Uffelman in his Ph.D. dissertation at California Institute of Technology (1992) and is the work upon which the synthesis of the journal article is based.)

Another synthetic route to the macrocycle is described in U.S. Pat. No. 5,853,428, issued also to the same Collins, and employs a ring forming strategy that is the reverse of the earlier published synthesis. In this synthesis, α -aminoisobutyric acid is used as a starting material to form the intermediate diacid 18 shown in Fig. 1, which is then coupled with an aryl diamine to yield the macrocycle (as shown in the scheme at col. 15 of the patent). This later synthesis, described by Collins as now being his preferred synthesis, provides the macrocycle structure in two steps and in an improved overall yield of about 18% (starting from diethyl malonyl dichloride). (Note: The identical synthesis is described by Scott W. Gordon-Wylie in his Ph.D. dissertation at Carnegie Mellon University (1995) and is the work upon which the synthesis of the patent is based.)

20 However, a number of problems exist with the Collins patent synthesis. For one, α -aminoisobutyric acid is a relatively expensive starting material. Further, the yield of the diacid is only about 50-60% from that starting material and usually requires further purification. Additionally, the first step, a double coupling, is said to require 72-144 hours for completion, while the second step, a ring closure, requires 48-110 hours. Still further, the use of large

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amounts of anhydrous pyridine as solvent are apparently required in both steps, which is commercially prohibitive. For commercial purposes, a more efficient and less expensive synthesis of the tetraamido macrocycle is required than is provided by either of the two prior art syntheses just described.

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SUMMARY OF THE INVENTION

Briefly, the present invention comprises an improved synthesis of tetraamido-macrocyclic ligands as exemplified by 5,6-benzo-3,8,11,13-tetraoxo-2,2,9,9-tetramethyl-12,12-diethyl-1,4,7,10-tetraazacyclotridecane, H₄. In the improved synthesis, a previously
10 unreported diamidodiol is formed in high yield from diethylmalonyl dichloride and the relatively inexpensive starting material 2-amino-2-methyl-1-propanol. The novel diamidodiol is then oxidized to the diacid used in the synthesis of the Collins patent described above. Coupling of the diacid with an aryl diamine then yields the macrocycle according to the procedure found in the same patent. However, in the improved synthesis of the present
15 invention, not only is a less expensive starting material used but the yield of the diacid is increased from the 50-60 % obtained in the prior art to approximately 74%. Additionally, the improved synthesis avoids the use of anhydrous pyridine solvent, which is also expensive. Further, the present invention produces an easily isolable product (i.e., the diacid) in excellent purity, whereas in the Collins patent the synthesis involves a tedious work-up procedure and
20 produces a product that typically requires recrystallization. The present invention requires that the intermediate diacid be made in two steps, but these steps are considerably more viable from a commercial standpoint than the Collins synthesis, both in terms of simplicity of performance and cost.

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BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a flowchart illustrating the improved synthesis of the tetraamido macrocycle using the novel diamidodiol precursor according to the present invention; and

Fig. 2 is a reaction sequence illustrating how variously substituted malonyl dichloride starting materials may be prepared.

DETAILED DESCRIPTION OF THE INVENTION

Fig. 1 illustrates a reaction sequence for preparing the tetraamido macrocycle 10 in a simpler and more commercially viable manner than has previously been reported. In the preferred reaction sequence, one mole of diethylmalonyl dichloride (dichloride 12) ($R^1=R^2$ =ethyl) is allowed to react with two to four moles of 2-amino-2-methyl-1-propanol (aminoalcohol 14) ($R^3=R^4$ =methyl) in an appropriate solvent. Ethyl acetate is the preferred solvent, however, other solvents such as tetrahydrofuran (THF), diethyl ether, acetonitrile or even water can also be used. 2-Amino-2-methyl-1-propanol is commercially available in large quantities, for example from Angus Chemical Company, and costs approximately \$1.65/pound. The relative inexpensiveness of the aminoalcohol 14 makes it an attractive starting material for preparing the macrocycle 10 in commercially viable quantities.

Ideally, four molar equivalents of the aminoalcohol 14 are employed in the reaction such that two moles are made to react with the dichloride 12 while the remaining two moles act as a base to scavenge the hydrogen chloride (HCl) that is generated during the reaction. A tertiary base such as triethylamine may also be used as an HCl scavenger, in which case only two molar equivalents of the aminoalcohol 14 are required. When ethyl acetate is used as the solvent, the desired product (diamidodiol 16), together with the ammonium salt produced by reaction of

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HCl with the aminoalcohol 14, precipitate from the reaction mixture. Thus, in what affords a highly desirable workup for commercial purposes, the solid products are simply collected by filtration and washed with water to remove the ammonium salt. After the washing, the remaining solid is the diamidodiol 16 in high purity and yield.

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With continued reference to Fig. 1, the diamidodiol 16 prepared in the previous step is suspended in an alkaline aqueous solution and is oxidized with potassium permanganate (KMnO_4) under controlled reaction temperature conditions to yield a mixture of the diacid 18 and manganese dioxide solids. Preferably the temperature of the reaction mixture is not allowed to exceed about 70 degrees C during the addition of the KMnO_4 . It will be appreciated that other oxidants known in the art can be used in place of KMnO_4 . After quenching the mixture with ethanol to destroy any excess KMnO_4 , the reaction mixture is filtered to remove the manganese dioxide solids. The filtrate is then strongly acidified, which causes precipitation of the diacid 18. The diacid 18 is collected by filtration and air-dried and is sufficiently pure to be used without further purification (the product is pure by ^{13}C -NMR). Thus, this second step again allows for a simple workup procedure and one that is industrially (and environmentally) very favorable. Actual examples of the procedures used for preparing compounds 16 and 18 are given later below.

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The diamidodiol 16 is a previously unreported compound. The ability to prepare the diamidodiol 16 in high yield and purity allows the diacid 18 to also be prepared in higher yield while using a starting material and solvents that are less expensive (and environmentally friendly), and with workup methods that are more amenable to commercial scale production

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than is possible with the prior art synthesis found in the Collins patent. This makes preparation of the macrocycle 10 in commercially reasonable amounts significantly more feasible.

As indicated in Fig. 1, the tetraamido macrocycle 10 itself is prepared by reaction of the diacid 18 with 1,2-phenylenediamine(phenylenediamine20) using the phosphorous trichloride (PCl₃) coupling method previously described in the Collins patent. Specifically, the diacid 18, phenylenediamine20 and pyridine are combined and heated to 50-60 degrees C. PCl₃ is then added and the mixture refluxed for forty-eight hours. The contents are acidified with HCl and extracted with methylene chloride. The combined organic layers are washed with dilute aqueous HCl followed by water. Rotary evaporation of the organic extracts yields the crude tetraamido macrocycle 10.

It will be apparent to those with ordinary skill in the art that the synthesis which has been described can easily be adapted for the preparation of tetraamido macrocyclic ligands having substituents other than that of the exemplified macrocycle 10. For example, in the first acylation step, a malonyl dihalide having R¹ and/or R² other than diethyl can be reacted with an aminoalcohol having R³ and/or R⁴ other than dimethyl to yield a variety of diamidodiol. (The synthesis of a number of variously disubstituted malonyl dichlorides is described later below.) Similarly, in the last coupling/cyclization step, a 1,2-phenylenediamine having substituents at any or all of the 3-, 4-, 5- and 6-positions of the phenyl ring can be employed to yield any number of what can generically be referred to as 1,2-bis(2-aminoalkanamido)benzenes. Thus, and referring to Fig. 1 one last time, R¹, R², R³ and R⁴ may be any of a wide variety of different substituents such as hydrogen, alkyl (including short and long chains), alkenyl, aryl (including benzyl), etc., and the phenyl ring

can be substituted with any of a number of substituents such as nitro, methoxy, halo, etc., as are all well known in the art, in order to make any number of differently substituted macrocycles 10.

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5 The following two examples illustrate the preferred methods for preparing compounds 16 and 18 according to the present invention:

EXAMPLE 1

Preparation of Diamidodiols (16)

10 2-Methyl-2-amino-1-propanol (42.9 grams, 0.482 moles) was dissolved in ethyl acetate (700 mL) in a 2 L round-bottom flask fitted with a mechanical stirrer. Diethylmalonyl dichloride (22.9 grams, 0.116 moles) was dissolved in ethyl acetate (30 mL) and added dropwise to the stirring solution of the aminoalcohol. A white precipitate begins to form immediately. After addition was complete, the reaction mixture was stirred for two hours at room temperature. Rotary evaporation of the solvent affords a white solid, which is shaken with water and filtered. The wet filter cake consisting of the crude product is used as-is in the next step.

EXAMPLE 2

Preparation of Diacid 18

20 The crude diamidodiols from Example 1 is slurried in water (300 mL). Sodium hydroxide (9.3 grams), predissolved in a small amount of water, is added to the slurry. The aqueous slurry is heated to about 50 degrees C and stirred vigorously. Powdered potassium permanganate (46 grams) is added in small portions at such a rate that the temperature of the reaction mixture does not exceed 70 degrees C. After the addition of the permanganate is complete, the mixture is heated for an additional hour at 60 degrees C. A small amount of ethanol is added to destroy any remaining permanganate and the reaction mixture is filtered through a plug of Celite. The clear filtrate is collected, cooled in an ice-bath, and acidified with concentrated HCl until the pH is less than 2. The white solid that precipitates is collected by filtration, washed well with water, and dried in a vacuum oven overnight. The final weight of the product is 28.4 grams (74% yield based upon starting malonyl dichloride). The product is pure by ¹³C-NMR and is identical to an authentic sample prepared by other means as indicated by NMR, IR, and melting point analyses.

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Figure 2 illustrates a synthetic route for the preparation of variously substituted malonyl dichlorides. The general synthetic procedure involves the stepwise alkylation of diethylmalonate(22). Diethylmalonate 22 is reacted in tetrahydrofuran(THF) with one equivalent of sodium hydride (NaH) and one equivalent of an alkylating agent such as an alkyl halide (e.g., R^1 -Br). The resulting monosubstituted diethylmalonate 24 is then reacted with a second equivalent of NaH and one equivalent of a second alkylating agent (e.g., R^2 -Br). (Note: Even when $R^1=R^2$, it is preferable that the first equivalent of NaH and the first equivalent of alkylating agent be allowed to react to completion before the second equivalent of NaH and the second equivalent of the same alkylating agent are added to the reaction mixture.) If the reaction is stopped before the second equivalents of reagents are added, then a monosubstituted malonate is obtained. The alkylation can be accomplished using other bases and solvents as are well-known in the art.

The disubstituted diethylmalonate (26) obtained from the stepwise alkylation is saponified using potassium hydroxide and ethanol and then chlorinated using thionyl chloride. The saponification can be accomplished using many other reagents, as are well-known in the art, and the chlorination can be accomplished with many other chlorinating agents, such as oxalyl chloride, PCl_3 , PCl_5 , etc.

The procedure outlined provides a general method for preparing substituted malonyl dichlorides 12 where R^1 and R^2 are the same or different. Examples 3, 4 and 5 below illustrate specific syntheses that utilize the reaction sequences illustrated in Fig. 2.

EXAMPLE 3 - ALKYLATIONS

Dipentyl diethylmalonate (26, R¹=R²=pentyl)

To a stirring solution of diethylmalonate (8.0 g, 50 mmol) in THF (100 mL, 0.5 M) was added sodium hydride (1.2 g, 50 mmol). The solution began bubbling and an exothermic reaction occurred. The reaction eventually turned clear and then pentyl bromide (6.2 mL, 50 mmol) was added. The reaction was refluxed for 20 hours and then cooled to room temperature. Another equivalent of NaH (1.2 g, 50 mmol) was added to the cloudy white mixture which was then stirred for 4 hours at room temperature. Another equivalent of pentyl bromide (6.2 mL, 50 mmol) was added and the reaction was refluxed for 20 hours. The reaction was cooled to room temperature and filtered to remove the precipitated sodium bromide. The mother liquor was collected and concentrated *in vacuo* to a yellow oil. The crude product was then distilled under vacuum (140°C) to afford 9.34 g (62%) of pure product.

Diocetyl diethylmalonate (26, R¹=R²=octyl)

To a stirring solution of diethylmalonate (16.0 g, 100 mmol) in THF (200 mL, 0.5 M) was added sodium hydride (2.4 g, 100 mmol). The solution began bubbling and an exothermic reaction occurred. The reaction eventually turned clear and then octyl bromide (17.3 mL, 100 mmol) was added. The reaction was refluxed for 20 hours and then cooled to room temperature. Another equivalent of NaH (2.4 g, 100 mmol) was added to the cloudy white mixture which was then stirred for 4 hours at room temperature. Another equivalent of octyl bromide (17.3 mL, 100 mmol) was added and the reaction was refluxed for 20 hours. The reaction was cooled to room temperature and filtered (NaBr). The mother liquor was collected and concentrated *in vacuo* to a yellow oil. The crude product was then distilled under vacuum (250°C) to afford 23.4 g (64%) of pure product.

Dodecylmethyl diethylmalonate (26, R¹=methyl, R²=dodecyl)

To a stirring solution of commercially available methyl diethylmalonate (17.4 g, 100 mmol) in THF (200 mL, 0.5 M) was added sodium hydride (2.4 g, 100 mmol). The solution began bubbling and an exothermic reaction occurred. The reaction eventually turned clear and then dodecyl bromide (24.0 mL, 100 mmol) was added. The reaction was refluxed for 20 hours and then cooled to room temperature and filtered (NaBr). The mother liquor was collected and concentrated *in vacuo* to a yellow oil. The crude product was then distilled under vacuum (239°C) to afford 17.7 g (52%) of pure product.

Hexadecylmethyl diethylmalonate (26, R¹=methyl, R²=hexadecyl)

To a stirring solution of methyl diethylmalonate (17.4 g, 100 mmol) in THF (200 mL, 0.5 M) was added sodium hydride (2.4 g, 100 mmol). The solution began bubbling and an exothermic reaction occurred. The reaction eventually turned clear and then hexadecyl bromide (30.5 mL, 100 mmol) was added. The reaction was refluxed for 20 hours and then cooled to room temperature and filtered (NaBr). The mother liquor was collected and concentrated *in vacuo* to a yellow oil. The crude product was then distilled under vacuum (275°C) to afford 13.8 g (35%) of pure product.

Methyloctyl diethylmalonate (26, R¹=methyl, R²=octyl)

To a stirring solution of methyl diethylmalonate (17.4 g, 100 mmol) in THF (200 mL, 0.5 M) was added sodium hydride (2.4 g, 100 mmol). The solution began bubbling and an exothermic reaction occurred. The reaction eventually turned clear and then octyl bromide

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(17.3 mL, 100 mmol) was added. The reaction was refluxed for 20 hours and then cooled to room temperature and filtered (NaBr). The mother liquor was collected and concentrated *in vacuo* to a yellow oil. The crude product was then distilled under vacuum (197°C) to afford 15.2 g (53%) of pure product.

5 Methylpentyl diethylmalonate (26, R¹=methyl, R²=pentyl)

To a stirring solution of methyl diethylmalonate, (17.4 g, 100 mmol) in THF (200 mL, 0.5 M) was added sodium hydride (2.4 g, 100 mmol). The solution began bubbling and an exothermic reaction occurred. The reaction eventually turned clear and then pentyl bromide (12.4 mL, 100 mmol) was added. The reaction was refluxed for 20 hours and then cooled to room temperature and filtered (NaBr). The mother liquor was collected and concentrated *in vacuo* to a yellow oil. The crude product was then distilled under vacuum (160°C) to afford 12.1 g (50%) of pure product.

EXAMPLE 4 - SAPONIFICATIONS

15 Dipentylmalonic acid

To a stirring mixture of dipentyl diethylmalonate (9.0 g, 30 mmol) in water (60 mL) and ethanol (60 mL) was added KOH pellets (16.8 g, 300 mmol). The cloudy mixture was then refluxed overnight where it became clear. The solvent was concentrated *in vacuo* to a white solid. The solid was dissolved in water and extracted with ether (2x). The water layer was then acidified with concentrated HCl and a solid precipitated out of solution. The white solid was filtered and the resulting mother liquor was extracted with ether in order to isolate any additional product. The combined organic layers were concentrated *in vacuo* and the resulting white solid was added to the filtered solid and dried in a vacuum oven. This afforded 5.6 g of pure product (76%).

25 Diocetylmalonic acid

To a stirring mixture of dioctyl diethylmalonate (15.0 g, 39 mmol) in water (78 mL) and ethanol (78 mL) was added KOH pellets (21.8 g, 390 mmol). The cloudy mixture was then refluxed overnight where it became clear. The solvent was concentrated *in vacuo* to a white solid. The solid was dissolved in water and extracted with ether (2x). The water layer was then acidified with concentrated HCl and a solid precipitated out of solution. The white solid was filtered and the resulting mother liquor was extracted with ether in order to isolate any additional product. The combined organic layers were concentrated *in vacuo* and the resulting white solid was added to the filtered solid and dried in a vacuum oven. This afforded 8.4 g of pure product (67%).

35 Dibenzylmalonic acid

To a stirring mixture of commercially available dibenzyl diethylmalonate (20.0 g, 64 mmol) in water (128 mL) and ethanol (128 mL) was added KOH pellets (35.9 g, 640 mmol). The cloudy mixture was then refluxed overnight where it became clear. The solvent was concentrated *in vacuo* to a white solid. The solid was dissolved in water and extracted with ether (2x). The water layer was then acidified with concentrated HCl and a solid precipitated out of solution. The white solid was filtered and the resulting mother liquor was extracted with ether in order to isolate any additional product. The combined organic layers were



CONSULADO DE COLOMBIA
WASHINGTON, D.C.



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No. 1400

EL CONSULADO DE COLOMBIA

CERTIFICA:

Que es auténtica la firma de FERNESIA L. CRAWFORD.
quien el día 5 DE JUNIO DEL 2000
desempeñaba las funciones de OFICIAL DE AUTENTICACIONES DEPARTAMENTO DE ESTADO.
la cual aparece al pie de los documentos anexos relacionados con APLICACION PARA PATENTE.

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JUNIO. del año dos mil (2000)

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Pagado Derecho Consular

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JAQUELINE ESPITIA ARIAS
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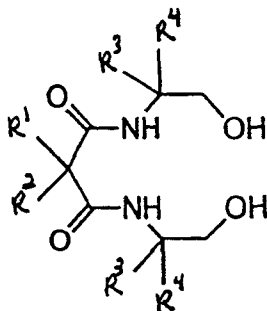
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CLAIMS

What is claimed is:

1. A chemical compound having the structural formula:

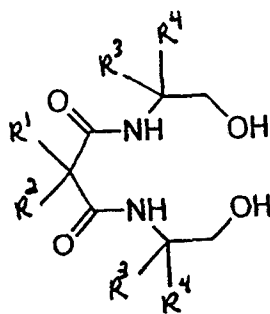


wherein R^1 , R^2 , R^3 and R^4 are the same or different and are selected from the group consisting of hydrogen, alkyl (including short and long chain), alkenyl, and aryl (including benzyl).

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2. The chemical compound of claim 1 wherein R^1 and R^2 are both ethyl.
3. The chemical compound of claim 1 wherein R^3 and R^4 are all methyl.
4. The chemical compound of claim 1 wherein R^1 and R^2 are the same and are selected from the group consisting of C_5H_{11} , C_8H_{17} , and $CH_2C_6H_5$.
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5. The chemical compound of claim 1 wherein R^1 is selected from the group consisting of C_5H_{11} , C_8H_{17} , $C_{12}H_{25}$, and $C_{16}H_{33}$, and R^2 is methyl.

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6. A method for synthesizing a diamidodiol having the structural formula:



5 wherein R¹, R², R³ and R⁴ are the same or different and are selected from the group consisting of hydrogen, alkyl (including short and long chain), alkenyl, and aryl (including benzyl), comprising:

10 forming a reaction solution comprised of a solvent, a first quantity of an aminoalcohol and a second quantity of a malonyl dichloride;

separating a product mixture from the reaction solution, the product mixture containing the diamidodiol; and

15 isolating the product diamidodiol from the product mixture.

7. The method of claim 6 wherein the reaction solution is formed by dissolving the first quantity of aminoalcohol in a first volume of the solvent to form a first solution; dissolving the second quantity of the malonyl dichloride in a second volume of the solvent to form a second solution; and

20 combining the first and second solutions to form the reaction solution.

8. The method of claim 7 where in the second solution is added dropwise to the first solution.

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9. The method of claim 6 wherein the first quantity and the second quantity provide a molar ratio of amino alcohol to malonyl dichloride in the range of approximately 2:1 to 4:1.

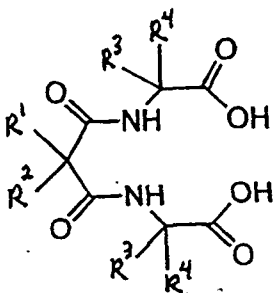
5 10. The method of claim 6 wherein the solvent is selected from the group consisting of ethyl acetate, tetrahydrofuran, diethyl ether, acetonitrile and water.

11. The method of claim 6 wherein the step of separating the product mixture from the reaction solution comprises evaporating the solvent.

10 12. The method of claim 6 wherein the step of separating the product mixture comprises filtration.

15 13. The method of claim 6 wherein the step of isolating the diamidodiols comprises washing the product mixture with water after the product mixture is separated from the reaction solution.

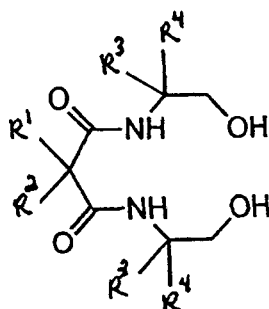
14. A method for preparing a diacid having the structural formula:



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comprising the step of:

oxidizing a diamidodiol having the structural formula



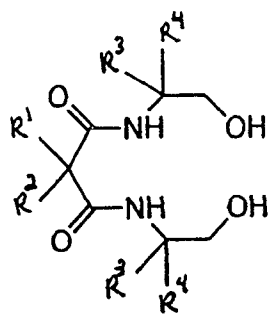
wherein R¹, R², R³ and R⁴ are the same or different and are selected from the group consisting of hydrogen, alkyl (including short and long chain), alkenyl, and aryl (including benzyl).

15. The method of claim 14 wherein the step of oxidizing the diamidodiol comprises adding KMnO₄ to an alkaline suspension comprised of the diamidodiol and water.

16. The method of claim 14 wherein the diamidodiol is prepared in prior steps comprising:
forming a reaction solution comprised of a solvent, a first quantity of an aminoalcohol and a second quantity of a malonyl dichloride;
separating a product mixture from the reaction solution; and
isolating the product diamidodiol from the product mixture.

17. A method for synthesizing a tetraamido-macrocyclecomprising:
synthesizing a diamidodiol having the structural formula

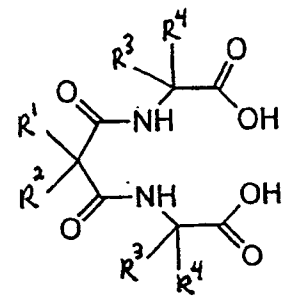
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wherein R^1 , R^2 , R^3 and R^4 are the same or different and are selected from the group consisting of hydrogen, alkyl (including short and long chain), alkenyl, and aryl (including benzyl);

oxidizing the diamidodiol to yield a diacid having the structural formula

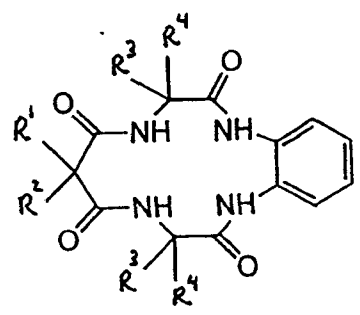


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forming a solution of the diacid and a 1, 2-diaminobenzene in pyridine to form a reaction solution; and

adding PCl_3 to the reaction solution to yield a tetraamido-macrocycle having the structural formula



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benzyl), and wherein the phenyl ring may be substituted or unsubstituted at any or all of the 3, 4, 5 and 6 ring positions.

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18. The method of claim 17 wherein the synthesizing of the diamidodiol comprises the reaction of an aminoalcohol with a malonyl dichloride.

19. The method of claim 17 wherein the step of oxidizing the diamidodiol comprises adding KMnO_4 to an alkaline suspension comprised of the diamidodiol and water.

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20. The method of claim 17 wherein the 1,2-diaminobenzene is unsubstituted at each of the 3, 4, 5 and 6 ring positions.

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ABSTRACT

A new composition of matter for a diamidodiol and a method for preparing the diamidodiol. The exemplary diamidodiol has the formula $C_{15}H_{30}N_2O_4$ and is prepared by
5 reacting a first quantity of 2-amino-2-methyl-1-propanol with a second quantity of a di-substituted malonyl dichloride (i.e., diethylmalonyl dichloride), preferably in ethyl acetate as solvent. A tetraamido macrocycle is prepared from the diamidodiol in two steps by oxidizing the diamidodiol to form a diacid followed by coupling using a known procedure of the diacid with an aryl diamine (e.g., 1,2-diaminobenzene) to yield the tetraamido macrocycle.

SECRET

DECLARATION FOR PATENT APPLICATION

As the below named inventors, we hereby declare that:

Our residences, post office addresses and citizenships are as stated below next to our names.

We believe we are the original, first and joint inventors of the subject matter which is claimed and for which a patent is sought on the invention entitled:

IMPROVED SYNTHESIS OF A TETRAAMIDO MACROCYCLE LIGAND FROM A NOVEL DIAMIDODIOL

the specification of which

 X is attached hereto
 was filed on _____
Application Serial No. _____
 and was amended on by amendment concurrently submitted herewith (if applicable)

We hereby state that we have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

We acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, Section 1.56(a).

We hereby claim the benefit under Title 35, United States Code Section 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application(s) in the manner provided by the first paragraph of Title 35, United States Code, Section 112, we acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, Section 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status-patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status-patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status-patented, pending, abandoned)

We hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent of Trademark Office connected therewith:

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OAKLAND, CA 94623-1305

We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Inventor's signature: Michael M. Ott

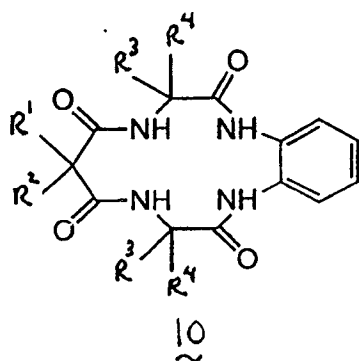
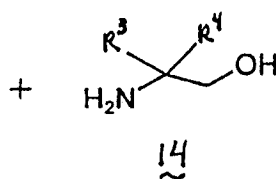
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File No.: 251.98

$$\begin{array}{c} \text{O} \\ \parallel \\ \text{R}^1 - \text{C} - \text{Cl} \\ | \\ \text{R}^2 - \text{C} - \text{Cl} \\ \parallel \\ \text{O} \end{array}$$


1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022 2023 2024 2025 2026 2027 2028 2029 2030 2031 2032 2033 2034 2035 2036 2037 2038 2039 2040 2041 2042 2043 2044 2045 2046 2047 2048 2049 2050 2051 2052 2053 2054 2055 2056 2057 2058 2059 2060 2061 2062 2063 2064 2065 2066 2067 2068 2069 2070 2071 2072 2073 2074 2075 2076 2077 2078 2079 2080 2081 2082 2083 2084 2085 2086 2087 2088 2089 2090 2091 2092 2093 2094 2095 2096 2097 2098 2099 2100 2101 2102 2103 2104 2105 2106 2107 2108 2109 2110 2111 2112 2113 2114 2115 2116 2117 2118 2119 2120 2121 2122 2123 2124 2125 2126 2127 2128 2129 2130 2131 2132 2133 2134 2135 2136 2137 2138 2139 2140 2141 2142 2143 2144 2145 2146 2147 2148 2149 2150 2151 2152 2153 2154 2155 2156 2157 2158 2159 2160 2161 2162 2163 2164 2165 2166 2167 2168 2169 2170 2171 2172 2173 2174 2175 2176 2177 2178 2179 2180 2181 2182 2183 2184 2185 2186 2187 2188 2189 2190 2191 2192 2193 2194 2195 2196 2197 2198 2199 2200 2201 2202 2203 2204 2205 2206 2207 2208 2209 2210 2211 2212 2213 2214 2215 2216 2217 2218 2219 2220 2221 2222 2223 2224 2225 2226 2227 2228 2229 2230 2231 2232 2233 2234 2235 2236 2237 2238 2239 2240 2241 2242 2243 2244 2245 2246 2247 2248 2249 2250 2251 2252 2253 2254 2255 2256 2257 2258 2259 2260 2261 2262 2263 2264 2265 2266 2267 2268 2269 2270 2271 2272 2273 2274 2275 2276 2277 2278 2279 2280 2281 2282 2283 2284 2285 2286 2287 2288 2289 2290 2291 2292 2293 2294 2295 2296 2297 2298 2299 2300 2301 2302 2303 2304 2305 2306 2307 2308 2309 2310 2311 2312 2313 2314 2315 2316 2317 2318 2319 2320 2321 2322 2323 2324 2325 2326 2327 2328 2329 2330 2331 2332 2333 2334 2335 2336 2337 2338 2339 2340 2341 2342 2343 2344 2345 2346 2347 2348 2349 2350 2351 2352 2353 2354 2355 2356 2357 2358 2359 2360 2361 2362 2363 2364 2365 2366 2367 2368 2369 2370 2371 2372 2373 2374 2375 2376 2377 2378 2379 2380 2381 2382 2383 2384 2385 2386 2387 2388 2389 2390 2391 2392 2393 2394 2395 2396 2397 2398 2399 2400 2401 2402 2403 2404 2405 2406 2407 2408 2409 2410 2411 2412 2413 2414 2415 2416 2417 2418 2419 2420 2421 2422 2423 2424 2425 2426 2427 2428 2429 2430 2431 2432 2433 2434 2435 2436 2437 2438 2439 2440 2441 2442 2443 2444 2445 2446 2447 2448 2449 2450 2451 2452 2453 2454 2455 2456 2457 2458 2459 2460 2461 2462 2463 2464 2465 2466 2467 2468 2469 2470 2471 2472 2473 2474 2475 2476 2477 2478 2479 2480 2481 2482 2483 2484 2485 2486 2487 2488 2489 2490 2491 2492 2493 2494 2495 2496 2497 2498 2499 2500 2501 2502 2503 2504 2505 2506 2507 2508 2509 2510 2511 2512 2513 2514 2515 2516 2517 2518 2519 2520 2521 2522 2523 2524 2525 2526 2527 2528 2529 2530 2531 2532 2533 2534 2535 2536 2537 2538 2539 2540 2541 2542 2543 2544 2545 2546 2547 2548 2549 2550 2551 2552 2553 2554 2555 2556 2557 2558 2559 2560 2561 2562 2563 2564 2565 2566 2567 2568 2569 2570 2571 2572 2573 2574 2575 2576 2577 2578 2579 2580 2581 2582 2583 2584 2585 2586 2587 2588 2589 2590 2591 2592 2593 2594 2595 2596 2597 2598 2599 2600 2601 2602 2603 2604 2605 2606 2607 2608 2609 2610 2611 2612 2613 2614 2615 2616 2617 2618 2619 2620 2621 2622 2623 2624 2625 2626 2627 2628 2629 2630 2631 2632 2633 2634 2635 2636 2637 2638 2639 2640 2641 2642 2643 2644 2645 2646 2647 2648 2649 2650 2651 2652 2653 2654 2655 2656 2657 2658 2659 2660 2661 2662 2663 2664 2665 2666 2667 2668 2669 2670 2671 2672 2673 2674 2675 2676 2677 2678 2679 2680 2681 2682 2683 2684 2685 2686 2687 2688 2689 2690 2691 2692 2693 2694 2695 2696 2697 2698 2699 2700 2701 2702 2703 2704 2705 2706 2707 2708 2709 2710 2711 2712 2713 2714 2715 2716 2717 2718 2719 2720 2721 2722 2723 2724 2725 2726 2727 2728 2729 2730 2731 2732 2733 2734 2735 2736 2737 2738 2739 2740 2741 2742 2743 2744 2745 2746 2747 2748 2749 2750 2751 2752 2753 2754 2755 2756 2757 2758 2759 2760 2761 2762 2763 2764 2765 2766 2767 2768 2769 2770 2771 2772 2773 2774 2775 2776 2777 2778 2779 2780 2781 2782 2783 2784 2785 2786 2787 2788 2789 2790 2791 2792 2793 2794 2795 2796 2797 2798 2799 2800 2801 2802 2803 2804 2805 2806 2807 2808 2809 2810 2811 2812

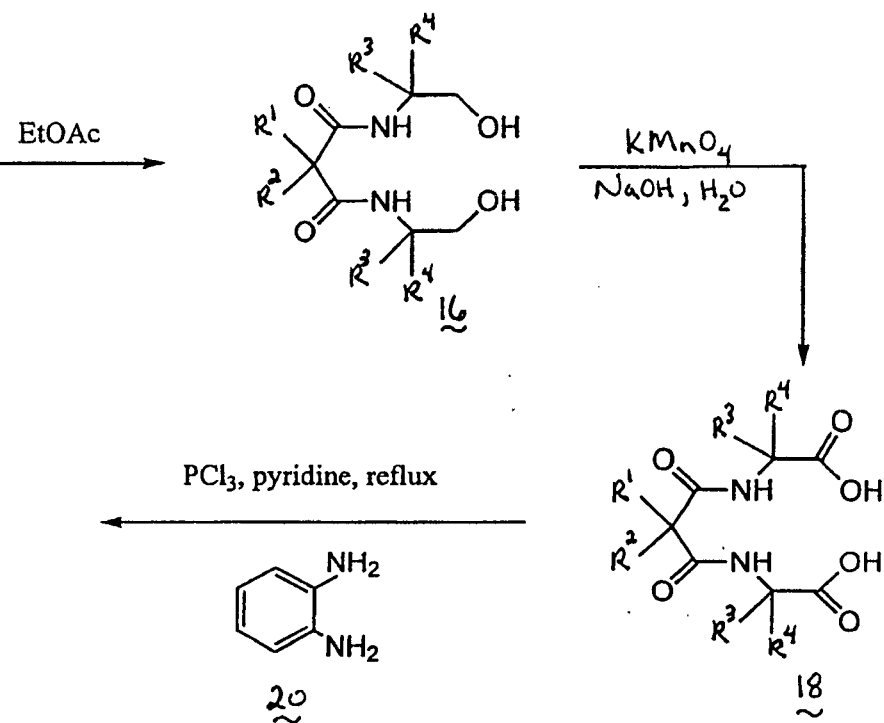


Fig. 1

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LOS ESTADOS UNIDOS DE AMERICA

A TODOS AQUELLOS A QUIENES LA PRESENTE VINIERE:

Departamento de Comercio de los Estados Unidos
Oficina de Patentes y Marcas de los Estados Unidos

Mayo 4, 2000

Por la presente se certifica que lo que obra anexo a ésta es copia fiel de los registros en la Oficina de Patentes y Marcas de los Estados Unidos de aquellos escritos de la solicitud de patente más adelante identificada que reunió los requisitos para que se le concediera una fecha de presentación sobre la base de 35 USC 111.

Número de Solicitud: 09/347,435

Fecha de Presentación: July 02, 1999

Por autoridad del
Comisionado de Patentes y Marcas

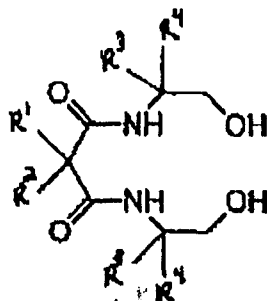
W. MONTGOMERY
Funcionario certificante

(Hay un sello-oblea)

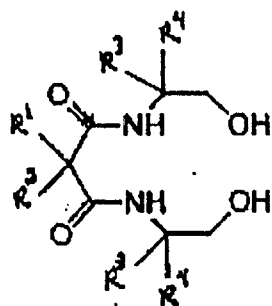
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Reivindicaciones

1. Un compuesto químico que tiene la fórmula estructural:



- en la cual R¹, R², R³ y R⁴ son iguales o diferentes, y se seleccionan del grupo formado por hidrógeno, alquilo (incluyendo los de cadena larga y corta), alquenilo, y arilo (incluyendo bencilo).
2. El compuesto químico de la reivindicación 1, en el cual R¹ y R² son ambos etilo.
3. El compuesto químico de la reivindicación 1, en el cual R³ y R⁴ son todos metilo.
4. El compuesto químico de la reivindicación 1, en el cual R¹ y R² son iguales y se seleccionan del grupo formado por C₅H₁₁, C₈H₁₇, y CH₂C₆H₅.
5. El compuesto químico de la reivindicación 1, en el cual R¹ se selecciona del grupo formado por C₅H₁₁, C₈H₁₇, C₁₂H₂₅, y C₁₆H₃₃ y R² es metilo.
6. Un método para sintetizar un diamidodiol que tiene una fórmula estructural:



en la cual R^1 , R^2 , R^3 y R^4 son iguales o diferentes, y se seleccionan del grupo formado por hidrógeno, alquilo (incluyendo los de cadena larga y corta), alquenoilo, y arilo (incluyendo bencilo), que comprende:

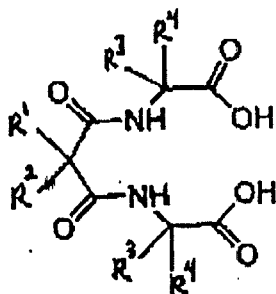
la formación de una solución de reacción que comprende un solvente, una primera cantidad de un amino alcohol y una segunda cantidad de un bicloruro de malonilo;

la separación de una mezcla producto de la solución de reacción, la mezcla producto contiene el diamidodiol; y

el aislamiento del producto diamidodiol de la mezcla producto.

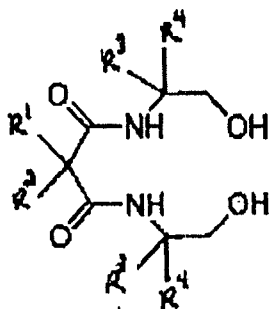
7. El método de la reivindicación 6, en el cual la solución de reacción se forma a partir de la disolución de la primera cantidad de amino alcohol en un primer volumen del solvente para formar una primera solución;
la disolución de una segunda cantidad del bicloruro de malonilo en un segundo volumen de solvente para formar una segunda solución; y
la combinación de la primera y segunda soluciones para formar la solución de reacción.
8. El método de la reivindicación 7, en el cual la segunda solución se agrega por goteo a la primera solución.
9. El método de la reivindicación 6, en el cual la primera cantidad y la segunda cantidad proporcionan un cociente molar de amino alcohol con relación al bicloruro de malonilo en el rango de , aproximadamente, 2:1 a 4:1.

- 41
93
10. El método de la reivindicación 6, en el cual el solvente se selecciona del grupo formado por acetato de etilo, tetrahidrofurano, éter dietílico, acetonitrilo y agua.
 11. El método de la reivindicación 6, en el cual la etapa de separación de la mezcla producto de la solución de reacción comprende la evaporación del solvente.
 12. El método de la reivindicación 6, en el cual la etapa de separación de la mezcla producto comprende filtración.
 13. El método de la reivindicación 6, en el cual la etapa de aislar el diamidodiol comprende el lavado de la mezcla producto con agua después de que la mezcla producto se separó de la solución de reacción.
 14. Un método de preparación de un diácido que tiene la fórmula estructural:



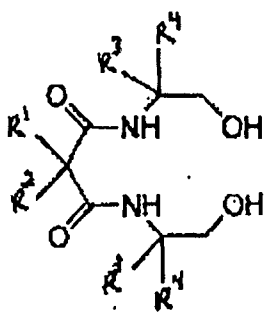
que comprende la etapa de:

oxidar un diamidodiol que tiene la fórmula estructural



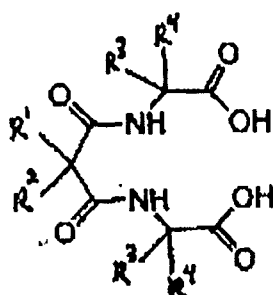
en la cual R^1 , R^2 , R^3 y R^4 son iguales o diferentes, y se seleccionan del grupo formado por hidrógeno, alquilo (incluyendo los de cadena larga y corta), alquenilo, y arilo (incluyendo bencilo).

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84
15. El método de la reivindicación 14 en el cual la etapa de oxidación del diamidodiol comprende el agregado de KMnO_4 a una suspensión alcalina que comprende el diamidodiol y agua.
16. El método de la reivindicación 14, en el cual el diamidodiol se prepara en etapas previas, que comprenden:
- la formación de una solución de reacción que comprende un solvente, una primera cantidad de un amino alcohol y una segunda cantidad de un bicloruro de malonilo;
 - la separación de una mezcla producto de la solución de reacción; y
 - el aislamiento del producto diamidodiol de la mezcla producto.
17. Un método para sintetizar un macrociclo de tetramido que comprende:
- sintetizar un diamidodiol que tiene la fórmula estructural



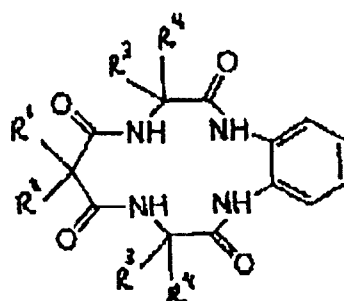
en la cual R^1 , R^2 , R^3 y R^4 son iguales o diferentes, y se seleccionan del grupo formado por hidrógeno, alquilo (incluyendo los de cadena larga y corta), alquenilo, y arilo (incluyendo bencilo);

oxidar el diamidodiol para obtener un diácido que tiene la fórmula estructural



formar una solución del diácido y un 1,2-diaminobenceno en piridina para formar una solución de reacción; y

agregar PCl_3 a la solución de reacción para obtener un macrociclo de tetramido que tiene la fórmula estructural



bencilo), y donde en anillo feñólico puede presentarse substituido o no en cualquiera o todas las posiciones 3, 4, 5 y 6 del anillo.

18. El método de la reivindicación 17, en el cual la síntesis del diamidodiol comprende la reacción de un amino alcohol con un bicloruro de malonilo.
19. El método de la reivindicación 17, en el cual la etapa de oxidación del diamidodiol comprende el ágregado de KMnO_4 a una suspensión alcalina que comprende el diamidodiol y agua.
20. El método de la reivindicación 17 en el cual el 1,2-diaminobenceno no se presenta substituido en cada una de las posiciones 3, 4, 5 y 6 del anillo.