(check at least one box)

a. ☒ Except as may be indicated below in (b), all of the patents, publications or other information are in the English language or were cited in an English language Search Report, a copy of which is attached hereto (concise explanation not required).

b. ☐ A concise explanation of the relevance of all patents, publications or other information listed that is not in the English language is as follows:

c. ☒ The following additional information is provided for the Examiner's consideration:

The listed reference was cited by the Chinese Patent Office in an Office Action dated December 12, 2003, in a corresponding application.

IV. THIS IDS IS BEING FILED UNDER 37 C.F.R. § 1.97(b)
(check one box)

a. ☐ within three months of the filing date of a national application (37 C.F.R. § 1.97(b) (1)). No fee or certification is required.

b. ☐ within three months of the date of entry of the national stage as set forth in §1.491 in an international application (37 C.F.R. § 1.97(b) (2)). No fee or certification is required.

c. ☐ before the mailing date of a first Action on the merits (37 C.F.R. § 1.97(b) (3)). No fee or certification is required. In the event that a first Office Action on the merits has been issued, please consider this IDS under 37 C.F.R. § 1.97(c) and see the certification under 37 C.F.R. § 1.97(e) below, or, if no certification has been made, charge our deposit account a fee in the amount of $240.00 as required by 37 C.F.R. § 1.17(p).

V. THIS IDS IS BEING FILED UNDER 37 C.F.R. § 1.97(c):
(check one box)

before the mailing date of a Final Office Action under 37 C.F.R. § 1.113 (See 37 C.F.R. § 1.97(c) (1)) or before the mailing date of a Notice of Allowance under 37 C.F.R. § 1.311 (See 37 C.F.R. § 1.97(c) (2)).

a. ☐ No certification; therefore, a fee in the amount of $180.00 is required by 37 C.F.R. § 1.17(p).
or

b. ☐ See the certification below. No fee is required.

VI. THIS IDS IS BEING FILED UNDER 37 C.F.R. § 1.97(d):
(check both boxes if applicable)

before payment of the Issue Fee (See 37 C.F.R. § 1.97(d).

a. ☒ See the certification below; and

b. ☒ A fee in the amount of $180.00 is enclosed as required by 37 C.F.R. § 1.17(p).

VII. CERTIFICATION UNDER 37 C.F.R. § 1.97(e) (check only one box)

The undersigned hereby certifies that

a. ☒ each item of information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application not more than three months prior to the filing of this IDS; or

b. ☐ no item of information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application or, to the best of my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this statement.

c. ☐ Some of the items of information were cited in a communication from a foreign Patent Office. As to this information, the undersigned certifies that each item of information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application not more than three months prior to the filing of this IDS. As to the remaining information, the undersigned hereby certifies that no item of this remaining information contained in the IDS was cited in a communication from a foreign Patent Office in a counterpart foreign application or, to the best of my knowledge after making reasonable inquiry, was known to any individual designated in 37 C.F.R. § 1.56(c) more than three months prior to the filing of this statement.

☐ Please charge Deposit Account No. 04-1105 in the amount of _____ for the above-indicated fee. A triplicate copy of this paper is attached.

☐ No fee is required.

If the Examiner has any questions concerning this IDS, he/she is requested to contact the undersigned. If it is determined that this IDS has been filed under the wrong rule, the PTO is requested to consider this IDS under the proper rule (with a petition, if necessary) and charge the appropriate fee to Deposit Account No. 04-1105.

Respectfully submitted,

Date: 2-12-04

Christine C. O'Day (Reg. No. 38,256)
EDWARDS & ANGELL, LLP
P.O. Box 55874
Boston, MA 02205
Tel: (617) 439-4444

Customer No. 21874

BOS2_433420.1

FORM PTO-1449 INFORMATION DISCLOSURE STATEMENT	ATTY DOCKET NO. 58827(45107)	SERIAL NO. 10/130,214
	APPLICANT(S): Claus Meese	
	FILING DATE: May 14, 2002	ART UNIT: 1624

UNITED STATES PATENT DOCUMENTS

EXAM. INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILE DATE IF APPR
	AA	5,686,464	11/11/97	R.A. Johansson et al.	514	315	

FOREIGN PATENT DOCUMENTS

		DOCUMENT NUMBER	PUBLISHED DATE	COUNTRY	CLASS	SUB CLASS	TRAN YES/NO

OTHER DOCUMENTS (INCLUDING AUTHOR, TITLE, DATE, PERTINENT PAGES, ETC.)

Examiner:	Date:

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

NOTICE OF ALLOWANCE AND FEE(S) DUE

7590 01/28/2004

Peter F. Corless
P O Box 9169
Boston, MA 02209

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 01/28/2004

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/130,214	05/14/2002	Claus Meese	41946/32854	9833

TITLE OF INVENTION: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$0	$1330	04/28/2004

THE APPLICATION IDENTIFIED ABOVE HAS BEEN EXAMINED AND IS ALLOWED FOR ISSUANCE AS A PATENT. PROSECUTION ON THE MERITS IS CLOSED. THIS NOTICE OF ALLOWANCE IS NOT A GRANT OF PATENT RIGHTS. THIS APPLICATION IS SUBJECT TO WITHDRAWAL FROM ISSUE AT THE INITIATIVE OF THE OFFICE OR UPON PETITION BY THE APPLICANT. SEE 37 CFR 1.313 AND MPEP 1308.

THE ISSUE FEE AND PUBLICATION FEE (IF REQUIRED) MUST BE PAID WITHIN THREE MONTHS FROM THE MAILING DATE OF THIS NOTICE OR THIS APPLICATION SHALL BE REGARDED AS ABANDONED. THIS STATUTORY PERIOD CANNOT BE EXTENDED. SEE 35 U.S.C. 151. THE ISSUE FEE DUE INDICATED ABOVE REFLECTS A CREDIT FOR ANY PREVIOUSLY PAID ISSUE FEE APPLIED IN THIS APPLICATION. THE PTOL-85B (OR AN EQUIVALENT) MUST BE RETURNED WITHIN THIS PERIOD EVEN IF NO FEE IS DUE OR THE APPLICATION WILL BE REGARDED AS ABANDONED.

HOW TO REPLY TO THIS NOTICE:

I. Review the SMALL ENTITY status shown above.

If the SMALL ENTITY is shown as YES, verify your current SMALL ENTITY status:
A. If the status is the same, pay the TOTAL FEE(S) DUE shown above.

B. If the status is changed, pay the PUBLICATION FEE (if required) and twice the amount of the ISSUE FEE shown above and notify the United States Patent and Trademark Office of the change in status, or

If the SMALL ENTITY is shown as NO:

A. Pay TOTAL FEE(S) DUE shown above, or

B. If applicant claimed SMALL ENTITY status before, or is now claiming SMALL ENTITY status, check the box below and enclose the PUBLICATION FEE and 1/2 the ISSUE FEE shown above.

☐ Applicant claims SMALL ENTITY status. See 37 CFR 1.27.

II. PART B - FEE(S) TRANSMITTAL should be completed and returned to the United States Patent and Trademark Office (USPTO) with your ISSUE FEE and PUBLICATION FEE (if required). Even if the fee(s) have already been paid, Part B - Fee(s) Transmittal should be completed and returned. If you are charging the fee(s) to your deposit account, section "4b" of Part B - Fee(s) Transmittal should be completed and an extra copy of the form should be submitted.

III. All communications regarding this application must give the application number. Please direct all communications prior to issuance to Mail Stop ISSUE FEE unless advised to the contrary.

IMPORTANT REMINDER: Utility patents issuing on applications filed on or after Dec. 12, 1980 may require payment of maintenance fees. It is patentee's responsibility to ensure timely payment of maintenance fees when due.

PTOL-85 (Rev. 11/03) Approved for use through 04/30/2004.

PART B - FEE(S) TRANSMITTAL

Complete and send this form, together with applicable fee(s), to: Mail **Mail Stop ISSUE FEE**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450
or Fax (703) 746-4000

INSTRUCTIONS: This form should be used for transmitting the ISSUE FEE and PUBLICATION FEE (if required). Blocks 1 through 4 should be completed where appropriate. All further correspondence including the Patent, advance orders and notification of maintenance fees will be mailed to the current correspondence address as indicated unless corrected below or directed otherwise in Block 1, by (a) specifying a new correspondence address; and/or (b) indicating a separate "FEE ADDRESS" for maintenance fee notifications.

CURRENT CORRESPONDENCE ADDRESS (Note: Legibly mark-up with any corrections or use Block 1)

7590 01/28/2004

Peter F. Corless
P O Box 9169
Boston, MA 02209

Note: A certificate of mailing can only be used for domestic mailings of the Fee(s) Transmittal. This certificate cannot be used for any other accompanying papers. Each additional paper, such as an assignment or formal drawing, must have its own certificate of mailing or transmission.

Certificate of Mailing or Transmission

I hereby certify that this Fee(s) Transmittal is being deposited with the United States Postal Service with sufficient postage for first class mail in an envelope addressed to the Mail Stop ISSUE FEE address above, or being facsimile transmitted to the USPTO, on the date indicated below.

(Depositor's name)

(Signature)

(Date)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/130,214	05/14/2002	Claus Meese	41946/32854	9833

TITLE OF INVENTION: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

APPLN. TYPE	SMALL ENTITY	ISSUE FEE	PUBLICATION FEE	TOTAL FEE(S) DUE	DATE DUE
nonprovisional	NO	$1330	$0	$1330	04/28/2004

EXAMINER	ART UNIT	CLASS-SUBCLASS
TUCKER, ZACHARY C	1624	514-530000

1. Change of correspondence address or indication of "Fee Address" (37 CFR 1.363).

❑ Change of correspondence address (or Change of Correspondence Address form PTO/SB/122) attached.

❑ "Fee Address" indication (or "Fee Address" Indication form PTO/SB/47; Rev 03-02 or more recent) attached. **Use of a Customer Number is required.**

2. For printing on the patent front page, list (1) the names of up to 3 registered patent attorneys or agents OR, alternatively, (2) the name of a single firm (having as a member a registered attorney or agent) and the names of up to 2 registered patent attorneys or agents. If no name is listed, no name will be printed.

1 _____

2 _____

3 _____

3. ASSIGNEE NAME AND RESIDENCE DATA TO BE PRINTED ON THE PATENT (print or type)

PLEASE NOTE: Unless an assignee is identified below, no assignee data will appear on the patent. Inclusion of assignee data is only appropriate when an assignment has been previously submitted to the USPTO or is being submitted under separate cover. Completion of this form is NOT a substitute for filing an assignment.

(A) NAME OF ASSIGNEE (B) RESIDENCE: (CITY and STATE OR COUNTRY)

Please check the appropriate assignee category or categories (will not be printed on the patent); ❑ individual ❑ corporation or other private group entity ❑ government

4a. The following fee(s) are enclosed:

❑ Issue Fee

❑ Publication Fee

❑ Advance Order - # of Copies _____

4b. Payment of Fee(s):

❑ A check in the amount of the fee(s) is enclosed.

❑ Payment by credit card. Form PTO-2038 is attached.

❑ The Director is hereby authorized by charge the required fee(s), or credit any overpayment, to Deposit Account Number _____ (enclose an extra copy of this form).

Director for Patents is requested to apply the Issue Fee and Publication Fee (if any) or to re-apply any previously paid issue fee to the application identified above.

(Authorized Signature) (Date)

NOTE: The Issue Fee and Publication Fee (if required) will not be accepted from anyone other than the applicant; a registered attorney or agent; or the assignee or other party in interest as shown by the records of the United States Patent and Trademark Office.

This collection of information is required by 37 CFR 1.311. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Alexandria, Virginia 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, Alexandria, Virginia 22313-1450.

Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMIT THIS FORM WITH FEE(S)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/130,214	05/14/2002	Claus Meese	41946/32854	9833

7590 01/28/2004

Peter F. Corless
P O Box 9169
Boston, MA 02209

EXAMINER	
TUCKER, ZACHARY C	
ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 01/28/2004

Determination of Patent Term Adjustment under 35 U.S.C. 154 (b)
(application filed on or after May 29, 2000)

The Patent Term Adjustment to date is 20 day(s). If the issue fee is paid on the date that is three months after the mailing date of this notice and the patent issues on the Tuesday before the date that is 28 weeks (six and a half months) after the mailing date of this notice, the Patent Term Adjustment will be 20 day(s).

If a Continued Prosecution Application (CPA) was filed in the above-identified application, the filing date that determines Patent Term Adjustment is the filing date of the most recent CPA.

Applicant will be able to obtain more detailed information by accessing the Patent Application Information Retrieval (PAIR) system (http://pair.uspto.gov).

Any questions regarding the Patent Term Extension or Adjustment determination should be directed to the Office of Patent Legal Administration at (703) 305-1383. Questions relating to issue and publication fee payments should be directed to the Customer Service Center of the Office of Patent Publication at (703) 305-8283.

PTOL-85 (Rev. 11/03) Approved for use through 04/30/2004.

Notice of Allowability	Application No.	Applicant(s)	
	10/130,214	MEESE, CLAUS	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *10 November 2003*.
2. ☒ The allowed claim(s) is/are *1-6,8-17,26 and 28-34*.
3. ☒ The drawings filed on 14 MAY '02 are accepted by the Examiner.
4. ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☒ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☒ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.
5. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
   (a) ☐ The translation of the foreign language provisional application has been received.
6. ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application. **THIS THREE-MONTH PERIOD IS NOT EXTENDABLE**

7. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.
8. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No. ____.
   (b) ☐ including changes required by the proposed drawing correction filed _____, which has been approved by the Examiner.
   (c) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No. _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the margin according to 37 CFR 1.121(d).

9. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1☐ Notice of References Cited (PTO-892)
2☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3☒ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No. 14May02
4☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5☐ Notice of Informal Patent Application (PTO-152)
6☐ Interview Summary (PTO-413), Paper No._____ .
7☒ Examiner's Amendment/Comment
8☒ Examiner's Statement of Reasons for Allowance
9☐ Other .

EXAMINER'S AMENDMENT

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone voicemail message from Christine C. O'Day 18 January 2004, which was in response to a message left by the examiner for Ms. O'Day on 16 January 2004.

IN THE SPECIFICATION –

Insert the heading "**Brief Description of the Drawing**" before the second to last paragraph on page 14 of the specification.

Response to Amendment

As requested in the correspondence from applicants dated 5 November 2003, which is in reply to the Office action of 4 August 2003, claims 3, 5, 6, 8 and 12-15 have been amended, claims 7, 18-25 and 27 have been cancelled and new claims 31-34 added.

Status of Claim Rejections - 35 USC § 112

In the previous Office action, dated 4 August 2003, claims 7, 18-25 and 27-30 were rejected under 35 U.S.C. 112, second paragraph, for indefiniteness.

Claims 7, 18-25 and 27 have been cancelled, mooting the rejection of that claim under this statute.

Claims 28-30 have been amended so as to define proper methods of manufacture under this statute, and therefore the rejection of claims 28-30 under 35 U.S.C. 112, second paragraph, is hereby withdrawn.

Status of Claim Rejections - 35 USC § 101

In the previous Office action, dated 4 August 2003 claims 21, 22 and 27-30 were rejected under 35 U.S.C. 101 for specifying non-statutory subject matter.

Claims 21, 22 and 27 have been cancelled, mooting the rejection of those claims under this statute.

Claims 28-30 have been amended so as to define proper methods of manufacture under this statute, and therefore the rejection of claims 28-30 under 35 U.S.C. 101 is hereby withdrawn.

Status of Obviousness-type Double Patenting

In the previous Office action, dated 4 August 2003, claims 1-7 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over allowed claims 3 and 4 of U.S. application no. 09/700,094.

The rejection is withdrawn in view of the Terminal Disclaimer over the commonly-owned cited application.

Status of Claim Rejections - 35 USC § 102

In the previous Office action, dated 4 August 2003, claims 18 and 23 were rejected as being anticipated by WO 94/11337 (Johansson et al).

Both claims 18 and 23 have been cancelled, mooting the rejection.

Status of Claim Rejections - 35 USC § 103

In the previous Office action, dated 4 August 2003, claims 20 and 25 were rejected under 35 U.S.C. 103(a) as being unpatentable over Johansson et al.

Both claims 20 and 25 have been cancelled, mooting the rejection.

In the previous Office action, dated 4 August 2003, claims 19 and 24 were rejected as being unpatentable over WO 98/43242 (Johansson et al '942).

Both claims 19 and 24 have been cancelled, mooting the rejection.

Allowable Subject Matter

Claims 1-6, 8-17, 26 and 28-34 are allowed.

The following is an examiner's statement of reasons for allowance:

All of the previously stated rejections have been obviated by cancellation of the rejected claim, or by amendment.

An updated search afforded no additional applicable prior art.

New claims 31-34 are patentable under 35 U.S.C. 112, first paragraph, as they comply with the written description and enablement requirement.

If not for the Terminal Disclaimer over 09/700,094, claims 31-34 would be the subject of an obviousness-type double patenting rejection over that application.

Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

Information Disclosure Statement

A PTO-1449 form, with a received dated of 14 May 2002, is enclosed herewith, initialed and signed.

Conclusion

All Post-Allowance Correspondence concerning this application must be mailed to:

Mail Stop Issue Fee
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Or you can fax them to the Office of Patent Publications at 703-308-5083, in order to expedite the handling of such correspondence as amendments under 37 CFR 1.312; information disclosure statements, and formal drawings. Sending Post-Allowance papers to Technology Center 1600 will only cause delays in matching papers with the case.

For information concerning status of correspondence sent after receipt of the Notice of Allowance, please contact the Correspondence Branch at (703) 305-8027.

The Notice of Allowance also has an insert containing contact information on other items, including Issue Fees, receipt of formal drawings and the status of the application.
zt

Richard L. Raymond
Primary Examiner
Art Unit 1624

10/130214

PTO/SB/42 (08-00) #3
Approved for use through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 199[redacted]ersons are required to respond to a collection of inf[redacted]n unless it displays a valid OMB control number.

JC13 Rec'd PCT/PTO 14 MAY 2002

Sheet 1 of 1

37 CFR 1.501 INFORMATION DISCLOSURE CITATION IN A PATENT (Use several sheets if necessary)	Docket Number (Optional) 41946/32854	Application Number ~~New~~ 10/130,214
	Applicant Claus Meese et al.	
	Filing Date Herewith	Group Art Unit ~~to be assigned~~ 1624

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	REF	DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

	REF	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB CLASS	TRANSLATION YES	TRANSLATION NO
ZT	BA	EP 0 667 852 B1	4/8/98	EPO	C07C 217	62	x	
ZT	BB	DE 693 17 898 T2	10/15/98	Germany	C07C 217	62	x	
ZT	BC	EP 0 957 073 A1	11/17/99	EPO	C07C1	00	x	

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER Zach Gu	DATE CONSIDERED 14 JANUARY 2004

Burden Hour Statement: This form is estimated to take 2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

1894918

Index of Claims

Application No.	Applicant(s)
10/130,214	MEESE, CLAUS
Examiner	**Art Unit**
Zachary C. Tucker	1624

√	Rejected	–	(Through numeral) Cancelled	N	Non-Elected	A	Appeal
=	Allowed	÷	Restricted	I	Interference	O	Objected

Claim		Date
Final	Original	1/2004
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Issue Classification	Application No.	Applicant(s)	
	10/130,214	MEESE, CLAUS	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

ISSUE CLASSIFICATION

ORIGINAL			CROSS REFERENCE(S)							
CLASS	SUBCLASS	CLASS	SUBCLASS (ONE SUBCLASS PER BLOCK)							
514	530	514	531	534	548	551				
INTERNATIONAL CLASSIFICATION		560	61	122	123	124	138	142	250	
A 01 N	37/08	564	319							
A 61 K	31/215									
A 01 N	37/12									
A 01 N	37/44									
A 61 N	31/124									

ZACHARY C. TUCKER
16 JAN. '04
(Assistant Examiner) (Date)

1/26/04
(LegalInstruments Examiner) (Date)

Acting SPE
Art Unit 1624
(Primary Examiner) (Date) 1-19-04

Total Claims Allowed: 24

O.G. Print Claim(s)	O.G. Print Fig.
1	1

☒ Claims renumbered in the same order as presented by applicant ☐ CPA ☐ T.D. ☐ R.1.47

Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original	Final	Original
	1		31		61		91		121		151		181
	2		32		62		92		122		152		182
	3		33		63		93		123		153		183
	4		34		64		94		124		154		184
	5		35		65		95		125		155		185
	6		36		66		96		126		156		186
	7		37		67		97		127		157		187
	8		38		68		98		128		158		188
	9		39		69		99		129		159		189
	10		40		70		100		130		160		190
	11		41		71		101		131		161		191
	12		42		72		102		132		162		192
	13		43		73		103		133		163		193
	14		44		74		104		134		164		194
	15		45		75		105		135		165		195
	16		46		76		106		136		166		196
	17		47		77		107		137		167		197
	18		48		78		108		138		168		198
	19		49		79		109		139		169		199
	20		50		80		110		140		170		200
	21		51		81		111		141		171		201
	22		52		82		112		142		172		202
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	24		54		84		114		144		174		204
	25		55		85		115		145		175		205
	26		56		86		116		146		176		206
	27		57		87		117		147		177		207
	28		58		88		118		148		178		208
	29		59		89		119		149		179		209
	30		60		90		120		150		180		210

Search Notes	Application No.	Applicant(s)	
	10/130,214	MEESE, CLAUS	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

SEARCHED			
Class	Subclass	Date	Examiner
514	530, 531, 534, 548, 551	1/16/04	ZT
560	61, 122, 123, 124, 138, 142, 250	1/16/04	ZT
564	319	1/16/04	ZT

INTERFERENCE SEARCHED			
Class	Subclass	Date	Examiner
514	530, 531, 534, 548, 551	1/16/04 ZT	
560	61, 122, 123, 124, 138, 142, 250		
564	319		

SEARCH NOTES (INCLUDING SEARCH STRATEGY)		
	DATE	EXMR
EAST – USPAT, USPG-PUB, EPO, JPO, DERWENT CLASS - SUBCLASSES X'D W/ "MUSCARINIC" AND "SALTS" AND "ESTERS"	1/16/04	ZT

1/prts

SPECIFICATION

ET 1/16/04 THIS APPLICATION WAS FILED UNDER 35 U.S.C. 371 AND IS THE U.S. NATIONAL STAGE OF PCT/EP00/11309, FILED 15 NOVEMBER 2000.

Stable salts of novel derivatives of 3,3-diphenylpropylamines

ins a'

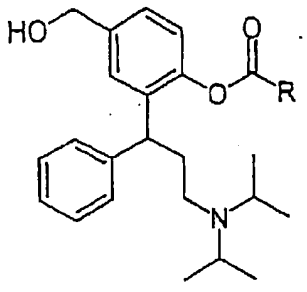
The present invention concerns highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, a method for manufacturing these and highly pure, stable, intermediate products.

From document PCT/EP99/03212 novel derivatives of 3,3-diphenylproprylamines are known.

These are valuable prodrugs for the treatment of urinary incontinence and other spasmodic complaints, which overcome the disadvantage of the active substances available to date, namely inadequate absorption of the active substance by biological membranes or the unfavourable metabolism of these.

Furthermore these novel prodrugs have improved pharmacokinetic characteristics compared with Oxybutynin and Tolterodin.

Preferred compounds from the group of these novel derivatives of 3,3-diphenylpropylamines are esters of aliphatic or aromatic carboxylic acids with the general formula A referred to below

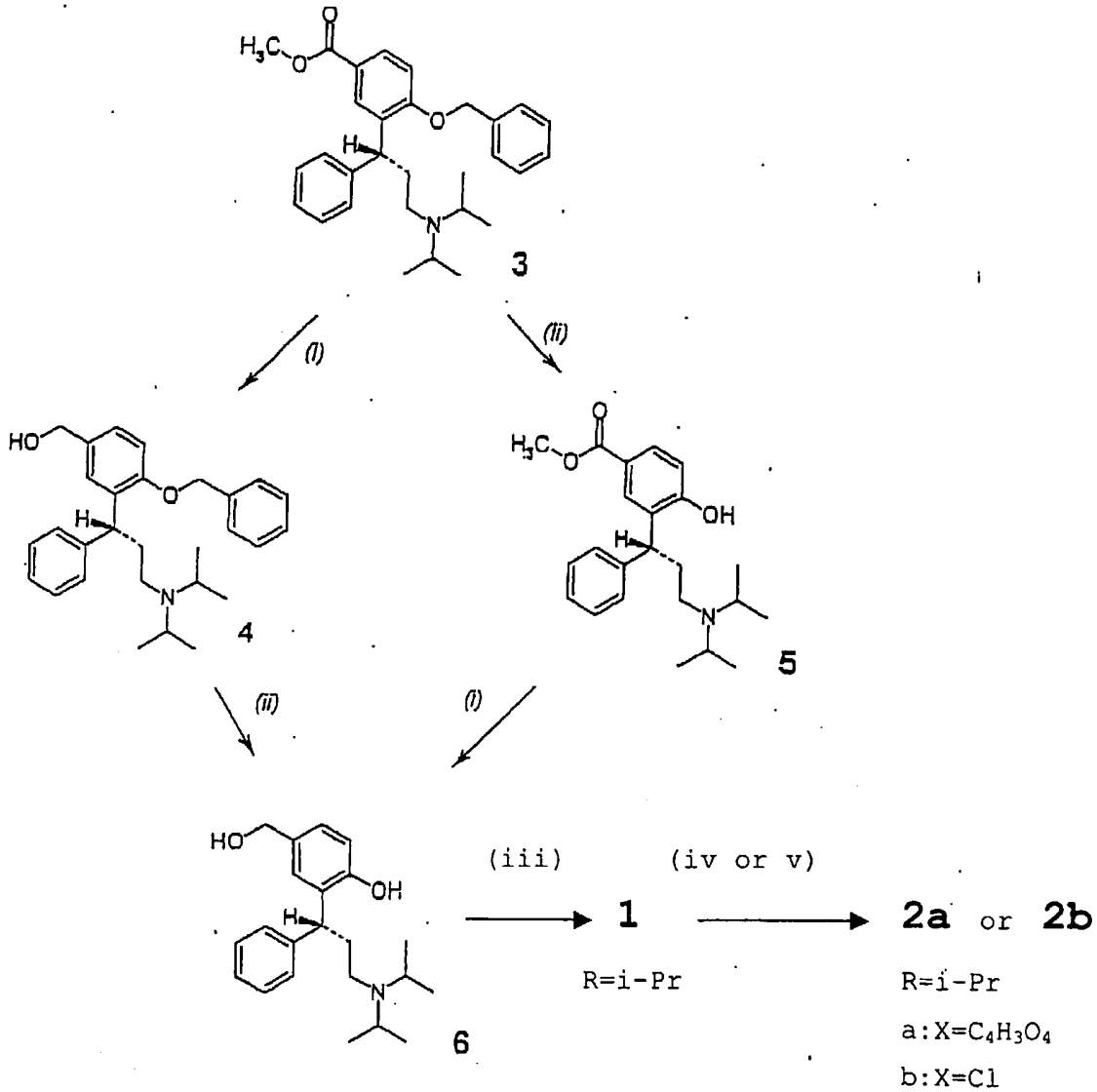


Formula A

Figure 1

Reaction diagram 1

(i), (ii), (iii), (iv), (v) stand for: (i), $LiAlH_4$, (ii), Raney nickel/H_2, (iii), Me_2CH-CoCl, Et_3N, (iv), fumaric acid, (v), hydrochloric acids; R stands for isopropyl (iPr)



PATENT APPLICATION FEE DETERMINATION RECORD
Effective October 1, 2001

Application or Docket Number: 10/130214

CLAIMS AS FILED - PART I

	(Column 1)		(Column 2)
TOTAL CLAIMS	30		
FOR	NUMBER FILED		NUMBER EXTRA
TOTAL CHARGEABLE CLAIMS	47	minus 20=	* 27
INDEPENDENT CLAIMS	10	minus 3 =	* 7
MULTIPLE DEPENDENT CLAIM PRESENT			☑

* If the difference in column 1 is less than zero, enter "0" in column 2

SMALL ENTITY TYPE ☐		OR	OTHER THAN SMALL ENTITY	
RATE	FEE		RATE	FEE
BASIC FEE	370.00	OR	BASIC FEE	~~740.00~~ 890
X$ 9=		OR	X$18=	486
X42=		OR	X84=	588
+140=		OR	+280=	280
TOTAL		OR	TOTAL	

CLAIMS AS AMENDED - PART II

AMENDMENT A

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	* 34	Minus	** 47	= 0
Independent	* 6	Minus	*** 10	= 0
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

SMALL ENTITY		OR	OTHER THAN SMALL ENTITY	
RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT B

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

AMENDMENT C

	(Column 1) CLAIMS REMAINING AFTER AMENDMENT		(Column 2) HIGHEST NUMBER PREVIOUSLY PAID FOR	(Column 3) PRESENT EXTRA
Total	*	Minus	**	=
Independent	*	Minus	***	=
FIRST PRESENTATION OF MULTIPLE DEPENDENT CLAIM				☐

RATE	ADDITIONAL FEE		RATE	ADDITIONAL FEE
X$ 9=		OR	X$18=	
X42=		OR	X84=	
+140=		OR	+280=	
TOTAL ADDIT. FEE		OR	TOTAL ADDIT. FEE	

* If the entry in column 1 is less than the entry in column 2, write "0" in column 3.
** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, enter "20."
*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, enter "3."
The "Highest Number Previously Paid For" (Total or Independent) is the highest number found in the appropriate box in column 1.

11-5-03

Practitioner's Docket No. 58827 (45107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	C. Meese		
Application No.:	10/130,214	GROUP:	1624
Filed:	May 14, 2002	EXAMINER:	Z. Tucker
For:	STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES		

Mail Stop: _____
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT TRANSMITTAL

1. Transmitted herewith is an amendment for this application.

STATUS

2. Applicant is
[ ] a small entity.
[X] other than a small entity.

CERTIFICATE OF MAILING/TRANSMISSION (37 C.F.R. 1.8(a))

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

[X] deposited with the United States Postal Service with sufficient postage as First Class Mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Date: 11/3/03

FACSIMILE

[ ] transmitted by facsimile to the Patent and Trademark Office.

Lee Dunkle
Signature

Lee Dunkle
(type or print name of person certifying)

NOTE: "Extension of Time in Patent Cases (Supplement Amendments) — If a timely and complete response has been filed after a Non-Final Office Action, an extension of time is not required to permit filing and/or entry of an additional amendment after expiration of the shortened statutory period.

If a timely response has been filed after a Final Office Action, an extension of time is required to permit filing and/or entry of a Notice of Appeal or filing and/or entry of an additional amendment after expiration of the shortened statutory period unless the timely-filed response placed the application in condition for allowance. Of course, if a Notice of Appeal has been filed within the shortened statutory period, the period has ceased to run." Notice of December 10, 1985 (1061 O.G. 34-35).

NOTE: See 37 C.F.R. 1.645 for extensions of time in interference proceedings, and 37 C.F.R. 1.550(c) for extensions of time in reexamination proceedings.

3. The proceedings herein are for a patent application and the provisions of 37 C.F.R. 1.136 apply.

(complete (a) or (b), as applicable)

(a) [ ] Applicant petitions for an extension of time under 37 C.F.R. 1.136 (fees: 37 C.F.R. 1.17(a)(1)-(4)) for the total number of months checked below:

	Extension (months)	Fee for other than small entity	Fee for small entity
[ ]	one month	$110.00	$55.00
[ ]	two months	$420.00	$210.00
[ ]	three months	$950.00	$475.00
[ ]	four months	$1,480.00	$740.00
[ ]	five months	$2,010.00	$1,005.00

Fee: $ _____

If an additional extension of time is required, please consider this a petition therefor.

(check and complete the next item, if applicable)

[ ] An extension for _____ months has already been secured. The fee paid therefor of $ _____ is deducted from the total fee due for the total months of extension now requested.

Extension fee due with this request $ _____

OR

(b) [X] Applicant believes that no extension of term is required. However, this conditional petition is being made to provide for the possibility that applicant has inadvertently overlooked the need for a petition for extension of time.

FEE FOR CLAIMS

4. The fee for claims (37 C.F.R. 1.16(b)-(d)) has been calculated as shown below:

(Col.1)		(Col. 2)	(Col. 3)	SMALL ENTITY			OTHER THAN A SMALL ENTITY	
Claims Remaining After Amendment		Highest No. Previously Paid For	Present Extra	Rate	Addit. Fee	*OR*	Rate	Addit. Fee
Total	* Minus	**	=	x $9 =	$0		x $18 =	$
Indep.	* Minus	***	=	x $42 =	$0		x $84 =	$ 0
[ ] First Presentation of Multiple Dependent Claim				+ $140 =	$0		+ $280 =	$ 0
				Total Addit. Fee	$	*OR*	Total Addit. Fee	$

* If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3,
** If the "Highest No. Previously Paid For" IN THIS SPACE is less than 20, enter "20".
*** If the "Highest No. Previously Paid For" IN THIS SPACE is less than 3, enter "3".
The "Highest No. Previously Paid For" (Total or Indep.) is the highest number found in the appropriate box in Col. 1 of a prior amendment or the number of claims originally filed.

WARNING: *"After final rejection or action (§ 1.113) amendments may be made canceling claims or complying with any requirement of form which has been made." 37 C.F.R. 1.116(a) (emphasis added).*

(complete (c) or (d), as applicable)

(c) [X] No additional fee for claims is required.

OR

(d) [ ] Total additional fee for claims required $ _____.

FEE PAYMENT

5. [X] Attached is a check in the sum of $ 110.00 (for the terminal disclaimer filed herewith).
[ ] Charge Account No. _____ the sum of $ _____.
A duplicate of this transmittal is attached.

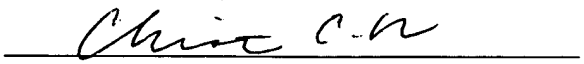
FEE DEFICIENCY

NOTE: If there is a fee deficiency and there is no authorization to charge an account, additional fees are necessary to cover the additional time consumed in making up the original deficiency. If the maximum, six-month period has expired before the deficiency is noted and corrected, the application is held abandoned. In those instances where authorization to charge is included, processing delays are encountered in returning the papers to the PTO Finance Branch in order to apply these charges prior to action on the cases. Authorization to charge the deposit account for any fee deficiency should be checked. See the Notice of April 7, 1986, (1065 O.G. 31-33).

6. [X] If any additional extension and/or fee is required, charge Account No. 04-1105.

AND/OR

[X] If any additional fee for claims is required, charge Account No. 04-1105.



SIGNATURE OF PRACTITIONER

Reg. No. 38,256

Christine C. O'Day
(type or print name of practitioner)

Tel. No. (617) 439-4444

EDWARDS & ANGELL, LLP
P.O. Box 9169
P.O. Address

Customer No. 21874

Boston, Massachusetts 02209

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Docket No. 58827 (45107)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	C. Meese		
SERIAL NO.:	10/130,214	ART UNIT:	1624
FILED:	May 14, 2002	EXAMINER:	Z. Tucker
FOR:	STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES		

Mail Stop: _____
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT

Applicants are in receipt of the Office Action dated August 4, 2003. Kindly amend the above-identified application as follows:

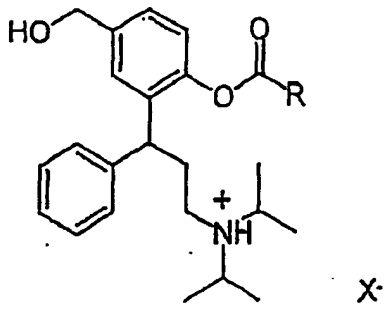
Amendments to the claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 14 of this paper.

This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of claims:

Claim 1 (original): Compounds of general formula I

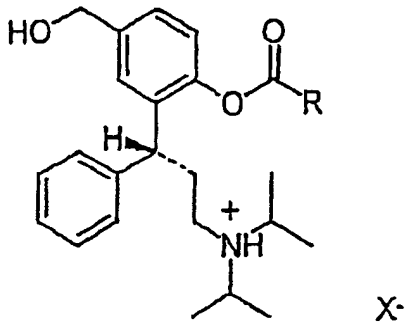


Formula I

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

Claim 2 (original): Compounds in accordance with claim 1, characterised in that X^- in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L- (-) -malic acid, D- (+) -malic acid, DL-tartaric acid, L- (+) -tartaric acid, D- (-) -tartaric acid, citric acid, L-aspartic acid, L- (+) -ascorbic acid, D- (+) - glucuronic acid, 2 - oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4 - hydroxybenzoic acid, salicyclic acid, vanillic acid, 4 - hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3- (4 - hydroxyphenyl) - propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

Claim 3 (currently amended): Compounds in accordance with claims 1 ~~and 2~~, characterised in that they have general formula 2.



Formula 2

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

Claim 4 (original): Compounds in accordance with claim 3, characterised in that X in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L- (-)-malic acid, D- (+) -malic acid, DL-tartaric acid, L- (+) - tartaric acid, D- (-) -tartaric acid, citric acid, L-aspartic acid, L- (+) -ascorbic acid, D- (+) - glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3 - (4 - hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

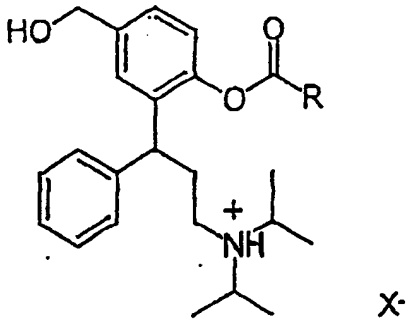
Claim 5 (currently amended): Compounds in accordance with claims 3 ~~and 4~~, characterised in that they are *R*- (+) – 2 - (3 - (diisopropylamino- 1 -phenylpropyl) – 4 – hydroxymethyl - phenylisobutyrate ester hydrogen fumarate, *R*- (+) – 2 - (3 - (diisopropylamino-l-phenylpropyl) – 4 - hydroxymethylphenylisobutyrate ester-hydrochloride hydrate.

Claim 6 (currently amended): Compounds in accordance with claims 3 ~~and 4~~, characterised in that *R* stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4 - (1-cyclopropyl-

methanoyloxy)-phenyl, 4 - (1 – cyclobutyl - methanoyloxy) - phenyl, 4 - (1 - cyclohexyl-methanoyloxy) -phenyl or 4 - (2, 2 – dimethyl -propanoyloxy) -phenyl and X^- denotes chloride.

Claim 7 (cancelled).

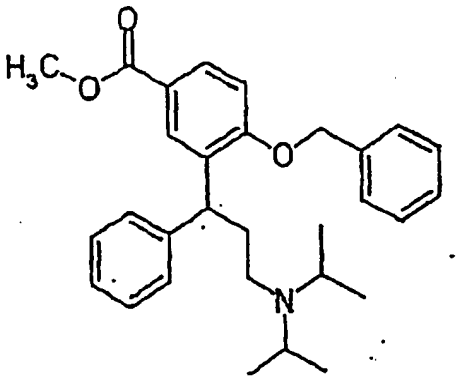
Claim 8 (currently amended): Method for manufacturing compounds of general formula I



Formula I

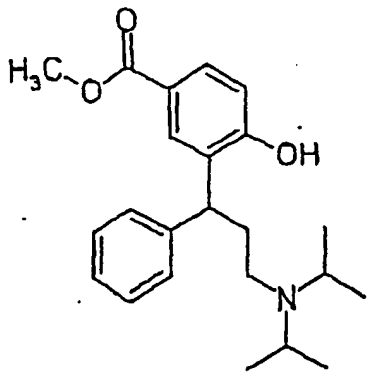
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid, characterised in that

a) a compound of formula III



Formula III

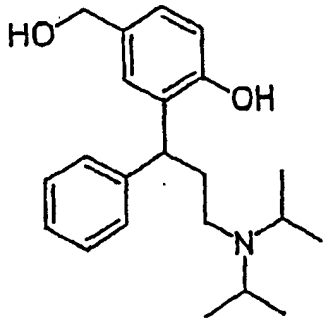
is split with a hydrogenation agent to form a compound of Formula V



Formula V

whereupon

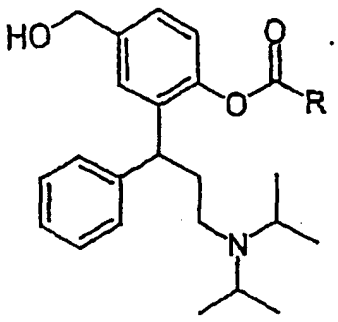
b) the compound of formula V so obtained is converted with a reducing agent, in order to give a compound of formula VI



Formula VI

which

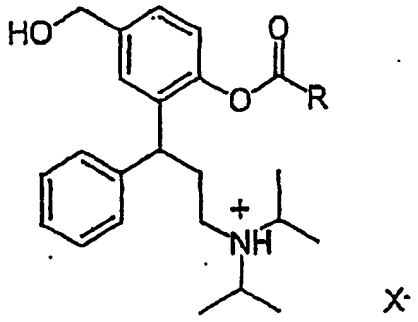
c) is converted with an acylation agent, in order to obtain a compound of formula A



Formula A

in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula I



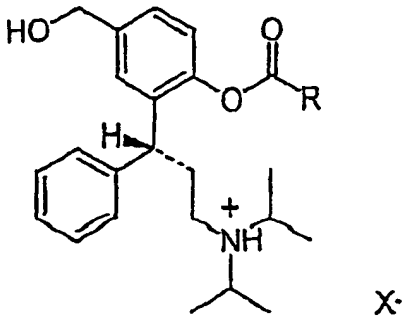
Formula I

in which R denotes C_1-C_6-alkyl, C_3-~~C10~~C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

Claim 9 (original): Method in accordance with claim 8, characterised in that for the manufacture of the compounds of general formula I hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L- (-) - malic acid, D- (+) - malic acid, DL-tartaric acid, L- (+) -tartaric acid, D- (-) -tartaric acid, citric acid, L-aspartic acid,

L- (+) -ascorbic acid, D- (+) -glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3- (4 - hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

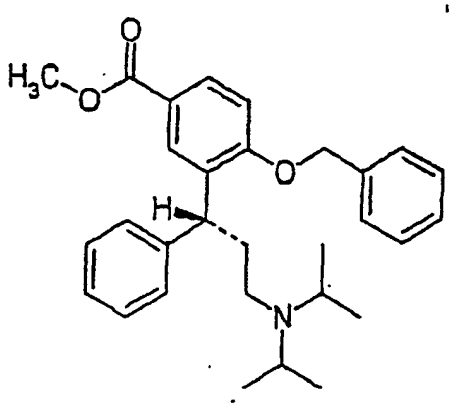
Claim 10 (original): Method for manufacturing compounds of general formula 2



Formula 2

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid, characterised in that

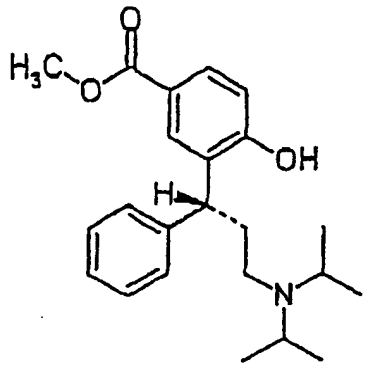
a) a compound of the formula 3



Formula 3

i

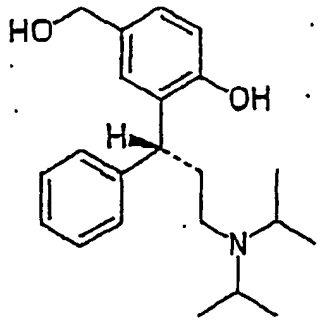
s split with a hydrogenation agent to form a compound of formula 5



Formula 5

whereupon

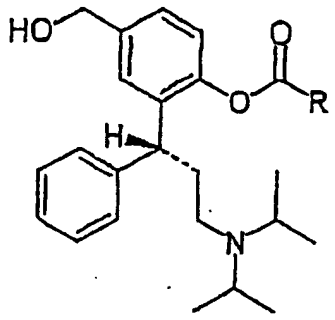
b) the compound of formula 5 so obtained is converted with a reducing agent, in order to give a compound of formula 6



Formula 6

which

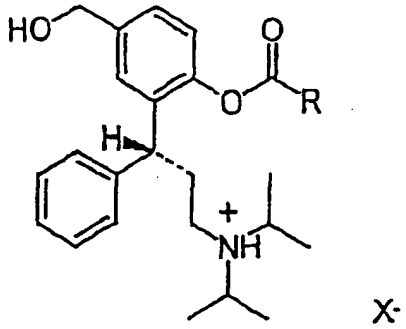
c) is converted with an acylation agent, in order to obtain a compound of formula 1



Formula 1

in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula 2



Formula 2

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

Claim 11 (original): Method in accordance with claim 10, characterised in that for the manufacture of the compounds of general formula 2 hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L- (-) -malic acid, D- (+) -malic acid, DL-tartaric acid, L- (+) -tartaric acid, D- (-) -tartaric acid, citric acid, L-aspartic acid,

L- (+) -ascorbic acid, D- (+) -glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3- (4 - hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

Claim 12 (currently amended): Method in accordance with claims 8 ~~to 11~~, characterised in that as the hydrogenation agent, Raney nickel/H_2 in methanol is preferably used as the solvent.

Claim 13 (currently amended): Method in accordance with claims 8 ~~to 11~~, characterised in that for the reducing agent $NaBH_4$/EtOH, preferably $LiAlH_4$/THF, is used.

Claim 14 (currently amended): Method in accordance with claims 8 ~~to 11~~, characterised in that for the acylation agent isobutyrylchloride and for the base triethylamine are used.

Claim 15 (currently amended): Method in accordance with claims 10 ~~to 14~~, characterised in that a compound of general formula 6 is converted with an equivalent isobutyryl chloride in the presence of triethylamine using one of the respective solvents ethylacetate, dichloromethane, tetrahydrofurane, acetonitrile or toluene regio- and chemoselectively into *R*- (+) -2-(3 - diisopropylamino-l-phenylpropyl) -4-hydroxymethylphenylisobutyrate.

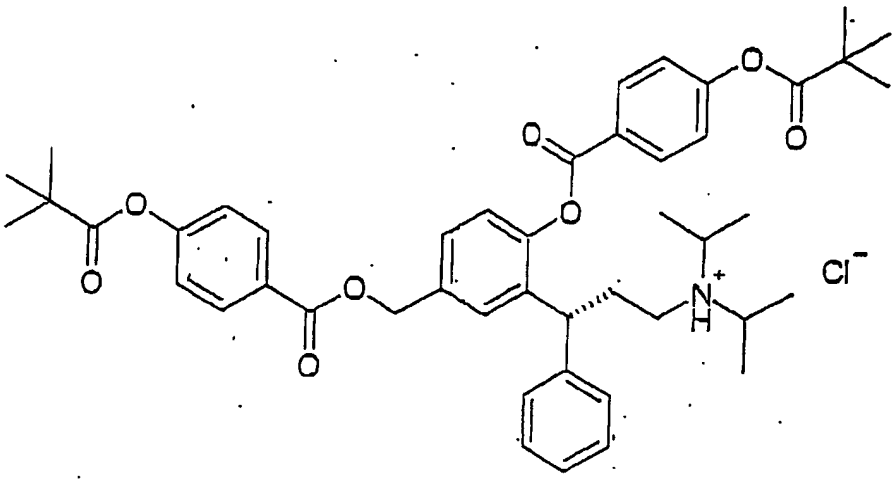
Claim 16 (currently amended): Method in accordance with claims 10 ~~to 15~~, characterised in that *R*- (+) -2-(3 - diisopropylamino-1-phenylpropyl) -4-hydroxymethylphenylisobutyrate ester and fumaric acid or hydrochloric acid are converted with the formation of the respective salt.

Claim 17 (currently amended): Method in accordance with claims 10 ~~to 13~~ for the manufacture of R-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-methylphenylisobutyrate ester hydrochloride hydrate, characterised in that the phenolic esterification of R-(+)-2-(3-

diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenol (6) is carried out without the addition of an external base, in that solutions of (6) are dropped into solutions of ~~isobutyrate~~ isobutyryl chloride, that contain at least 1 mole equivalent of water, in order to directly obtain a corresponding stable, hydrate-containing hydrochloride.

Claims 18-25 (cancelled).

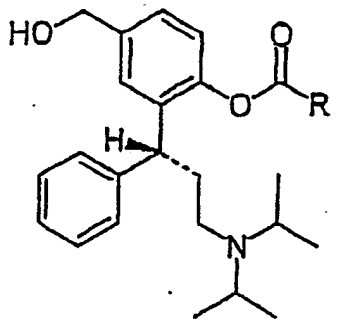
Claim 26 (original): Compound of formula 7



Formula 7

Claim 27 (cancelled).

Claim 28 (currently amended): ~~A method of Use of a compound in accordance with claims 23 to 26 as an intermediate product in the~~ manufacture of phenolic monoesters of general formula 1



Formula 1

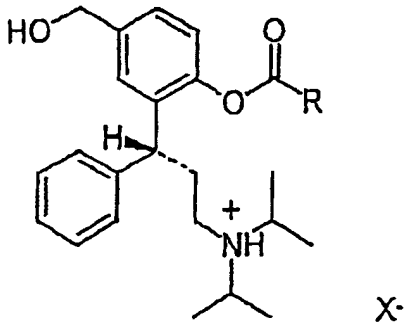
wherein the method comprises the steps of:

providing a compound of claim 26;

deprotecting the hydroxyl residues of the 4-hydroxy-benzyl alcohol residue; and

acylating the phenol residue.

Claim 29 (currently amended): A method of ~~Use of a compound in accordance with claims 23 to 26 as an intermediate product in the~~ manufacture of salts of phenolic monoesters of general formula 2:



Formula 2

---

in which R ~~has the same meaning as given in claim 3~~ denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid, wherein the method comprises the steps of:

providing a compound of claim 26;

deprotecting the hydroxyl residues of the 4-hydroxy-benzyl alcohol residue; and

acylating the phenol residue.

Claim 30 (currently amended): A method of ~~Use of a compound in accordance with claims 23 to 26 as an intermediate product in the~~ manufacture of *R*- (+) -2- (3-diisopropylamino-l-phenylpropyl) -4-hydroxymethylphenylisobutyrate ester hydrogen fumarate ~~and~~ or *R*- (+) -2- (3-diisopropylamino-l-phenylpropyl) -4- hydroxymethylphenylisobutyrate ester hydrochloride hydrate, the method comprising the steps of:

providing a compound of claim 26;

deprotecting the hydroxyl residues of the 4-hydroxy-benzyl alcohol residue; and

acylating the phenol residue.

Claim 31 (new): A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 1.

Claim 32 (new): A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 3.

Claim 33 (new): A method of treating a patient suffering from urinary incontinence, which method comprises the step of administering to said patient an effective amount of a compound according to claim 5.

Claim 34 (new): The method of any one of claims 31-33, wherein the urinary incontinence disorder is urge incontinence.

REMARKS

Claims 3, 5, 6, 8, 12-17, and 28-30 have been amended; claims 7, 18-25, and 27 stand cancelled; and new claims 31-34 are added. No new matter has been added by virtue of the within amendment. Support for the amended and newly presented claims appears throughout the specification and in the original claims of the application.

As an initial matter, Applicants appreciate the indication of allowable subject matter, i.e., that claims 8-11 and 26 stand allowed, and that claims 12-17 would be allowable if amended to correct improper multiple dependencies and other minor informalities.

Referring now to the Office Action, claims 7, 18-25, and 27-30 stand rejected under 35 USC §112, 2nd paragraph.

Applicants believe that the subject matter of the noted claims is indeed clear and definite. However, in an effort to expedite allowance of the application, each of the noted claims has been cancelled or amended to further define the present invention. For instance, claims 28-30 have been amended to provide method of preparation claims. Withdrawal of the rejection is therefore proper.

Claims 21, 22 and 27-30 stand rejected under 35 USC §101.

Again, in an effort to expedite allowance of the application, claims 21, 22, and 27 have been cancelled and claims 28-30 have been amended to provide method of preparation claims. Withdrawal of the rejection is therefore proper.

Claims 1-7 stand rejected under the judicially created doctrine of obviousness-type double patenting over copending application USSN 09/700,094. Applicants confirm that the cited application and the present application are commonly owned. Additionally, in order to

obviate the rejection, Applicants enclose herewith a terminal disclaimer. Withdrawal of the rejection is therefore proper.

The remaining rejections relate to the prior art and are summarized as follows.

Claims 18 and 23 stand rejected under 35 USC §102(b) over WO 94/11337 (Johansson et al.).

Claims 20 and 25 stand rejected under 35 USC §103(a) over WO 94/11337 (Johansson et al.).

Claims 19 and 24 stand rejected under 35 USC §103(a) over WO 98/43942 (Johansson et al. '942).

The rejections are traversed. Applicants submit that the cited references do not teach or suggest the present invention in a manner sufficient to sustain the instant rejection. For example, see *In re Marshall*, 198 USPQ 344, 346 (CCPA 1978) ("[r]ejections under 35 U.S.C. §102 are proper only when the claimed subject matter is identically disclosed or described in the prior art.") Additionally, it is well-known that to establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference(s) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). See MPEP § 2143.

Nonetheless, in an effort to expedite allowance of the application, the rejected claims

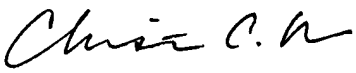
have been cancelled. Withdrawal of the rejection is therefore proper.

It also is noted that claims 3 and 5-6 have been amended to remove improper multiple dependencies. Withdrawal of the objections related to those claims is requested.

Lastly, claim 8 has been amended merely to correct a typographical error.

It is believed the application is in condition for immediate allowance, which action is earnestly solicited.

Respectfully submitted,



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Tel. (617) 439-4444

Practitioner's Docket No. 58827 (45107) ***PATENT***

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	C. Meese		
Application No.:	10/130,214	GROUP:	1624
Filed:	May 14, 2002	EXAMINER:	Z. Tucker
For:	STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES		
[ ] *Patent No.:	Issue Date: Reexamination Date:		

**NOTE: Preferably also insert inventor's name and invention title.*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

TERMINAL DISCLAIMER TO OBVIATE A DOUBLE PATENTING REJECTION (37 C.F.R. SECTION 1.321(c))

Identification of Person(s) Making This Disclaimer

I, Christine C. O'Day

CERTIFICATE OF MAILING/TRANSMISSION (37 C.F.R. SECTION 1.8(a))

I hereby certify that, on the date shown below, this correspondence is being:

MAILING	FACSIMILE
[X] deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.	[ ] transmitted by facsimile to the Patent and Trademark Office, (703) ___-____.

11/06/2003 SDENBOB1 00000030 10130214
01 FC:1814 110.00 OP

Signature

Date: November 3, 2003

Lee Dunkle
(type or print name of person certifying)

(type or print names of all inventors or assigns or name of attorney signing disclaimer)

(a) represent that I am

[ ] an inventor (applicant) of this invention.

[ ] an assignee of this invention.

WARNING: *"If the patent or patent application is assigned to an organization, such as a corporation, partnership, university, [g]overnment agency or similar entity, and the disclaimer is signed by the assignee, the assignee must comply with Section 3.73(b)." Notice of Oct. 15, 1993, 1156 O.G. 54-61 at 56, Section 1490, M.P.E.P., 7th Edition.*

[ ] a representative authorized to sign on behalf of the assignee identified below.

[ ] A statement under 37 C.F.R. Section 3.73(b) is attached.

WARNING: *See the above "WARNING".*

[X] the attorney of record for this invention.

NOTE: The rules "permit an attorney or agent of record to sign a terminal disclaimer without the need to comply with Section 3.73(b)." Notice of Oct. 15, 1993, 1156 O.G. 54-61, at 56. See also Section 1490, M.P.E.P., 7th Edition.

IDENTITY OF ASSIGNEE AND TITLE OF DISCLAIMANT
(if applicable)

The assignee is

Name of assignee Schwarz Pharma AG

Address of assignee Alfred-Nobel-Strasse 10, 40789 Monheim, Germany

Title of disclaimant authorized to sign on behalf of assignee n/a

EXTENT OF DISCLAIMANT'S INTEREST

The extent of the interest in this invention that the disclaimant owns is in:

[X] the whole of this invention.

[ ] a sectional interest in this invention, as follows:

(state the exact interest of the disclaimant)

RECORDAL OF ASSIGNMENT IN PTO
(if applicable)

[X] The assignment was recorded on: May 14, 2002

Reel 013122
Frame 0883

[ ] Authorization for recordal of the assignment is separately attached.

[ ] A separate [ ] "ASSIGNMENT (DOCUMENT) COVER SHEET" or
[ ] FORM PTO 1595 is also attached.

ESTABLISHING RIGHT OF ASSIGNEE TO TAKE ACTION
(if applicable)

[ ] Attached is a STATEMENT UNDER 37 C.F.R. Section 3.73(b) establishing the right of the assignee to take action in this case.

DISCLAIMER
(select one of the following)

(Provisional Obviousness-Type Double Patenting Rejection Over A Pending Application)

Petitioner hereby disclaims, except as provided below, the terminal part of any patent granted on the instant application, which would extend beyond the expiration date of any patent granted on Application No. 09/700,094, filed on January 2, 2001, as shortened by any terminal disclaimer. Petitioner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and any patent granted on the above-listed application are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors, or assigns.

In making the above disclaimer, disclaimant does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. Sections 154 to 156 and 173 of any patent granted on the application forming the basis of the double patenting rejection, namely, any patent granted on Application No.: 09/700,094, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of

competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. Section 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to expiration of its full statutory term as presently shortened by any terminal disclaimer, except for the separation of legal title stated above.

DISCLAIMER FEE (37 C.F.R. Section 1.20(d))

[X] Other than a small entity--fee $110.00

[ ] Small entity--fee $55.00

[ ] Small entity statement attached
[ ] Small entity statement already filed
[ ] in patent application __/ _____ on
(date)

OR

(Obviousness-Type Double Patenting Rejection Over A Prior Patent)

Petitioner hereby disclaims, except as provided below, the terminal part of any patent granted on the instant application, which would extend beyond the expiration date of Patent No. _____ as presently shortened by any terminal disclaimer. Petitioner hereby agrees that any patent so granted on the instant application shall be enforceable only for and during such period that it and the above-listed patent are commonly owned. This agreement runs with any patent granted on the instant application and is binding upon the grantee, its successors, or assigns.

In making the above disclaimer, disclaimant does not disclaim the terminal part of any patent granted on the instant application that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. Sections 154 to 156 and 173 of the patent forming the basis of the double patenting rejection, namely, Patent No.: _____, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. Section 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to expiration of its full statutory term as presently shortened by any terminal disclaimer, except for the separation of legal title stated above.

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[ ] Small entity--fee $55.00

[ ] Small entity statement attached
[ ] Small entity statement already filed

[ ] in patent application __/_____ on

(date)

OR

(Provisional Obviousness-Type Double Patenting Rejection Over A Pending Application--Reexamination Proceeding)

Petitioner hereby disclaims, except as provided below, the terminal part of any patent being reexamined, which would extend beyond the expiration date of any patent granted on Application No. __/_____, filed on _____, as shortened by any terminal disclaimer. Petitioner hereby agrees that any reexamination certificate issued on the instant patent being reexamined shall be enforceable only for and during such period that it and any patent granted on the above-listed application are commonly owned. This agreement runs with any reexamination certificate issued on the instant patent granted and is binding upon the grantee, its successors, or assigns.

In making the above disclaimer, disclaimant does not disclaim the terminal part of any reissue certificate granted on the instant patent being reexamined that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. Sections 154 to 156 and 173 of any patent granted on the application forming the basis of the double patenting rejection, namely, any patent granted on Application No.: ____/ _____, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. Section 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to expiration of its full statutory term as presently shortened by any terminal disclaimer, except for the separation of legal title stated above.

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[ ] Other than a small entity--fee $110.00

[ ] Small entity--fee $55.00

[ ] Small entity statement attached
[ ] Small entity statement already filed
[ ] in patent application __/ _____ on

(date)

OR

(Provisional Obviousness-Type Double Patenting Rejection Over A Prior Patent--Reexamination Proceeding)

Petitioner hereby disclaims, except as provided below, the terminal part of the patent being reexamined, which would extend beyond the expiration date of Patent No. _____ as presently shortened by any terminal disclaimer. Petitioner hereby agrees that the patent for which a reexamination certificate is issued as a result of this proceeding shall be enforceable only for and during such period that it and the above listed patent granted are commonly owned. This agreement runs with any reexamination certificate issued on the instant patent and is binding upon the grantee, its successors, or assigns.

In making the above disclaimer, disclaimant does not disclaim the terminal part of any reexamination certificate granted on the instant patent that would extend to the expiration date of the full statutory term as defined in 35 U.S.C. Sections 154 to 156 and 173 of the patent forming the basis of the double patenting rejection, namely, Patent No.: _____, as presently shortened by any terminal disclaimer, in the event that it later: expires for failure to pay a maintenance fee, is held unenforceable, is found invalid by a court of competent jurisdiction, is statutorily disclaimed in whole or terminally disclaimed under 37 C.F.R. Section 1.321, has all claims cancelled by a reexamination certificate, is reissued, or is in any manner terminated prior to expiration of its full statutory term as presently shortened by any terminal disclaimer, except for the separation of legal title stated above.

DISCLAIMER FEE (37 C.F.R. Section 1.20(d))

[ ] Other than a small entity--fee $110.00

[ ] Small entity--fee $55.00

[ ] Small entity statement attached
[ ] Small entity statement already filed
[ ] in patent application __/_____ on
(date)

FEE PAYMENT

[X] Attached is a check in the sum of $ 110.00.

[X] Charge Account 04-1105 for any fee deficiency.

[ ] Charge Deposit Account _____ the sum of $_____.
A duplicate of this disclaimer is attached.

Signature of disclaimant

Date: 11-3-03

Christine C. O'Day

SIGNATURE OF PRACTITIONER

Reg. No.: 38,256

Christine C. O'Day (Reg. No.: 38,256)
EDWARDS & ANGELL, LLP
P.O. Box 9169
Boston, MA 02209
Tel. (617) 439-4444

Customer No.: 21874

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/130,214	05/14/2002	Claus Meese	41946/32854	9833

7590 08/04/2003

Peter F. Corless
P O Box 9169
Boston, MA 02209

EXAMINER
TUCKER, ZACHARY C

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 08/04/2003

10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/130,214	MEESE, CLAUS	
	Examiner	Art Unit	
	Zachary C. Tucker	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *8-11 and 26* is/are allowed.

6)☒ Claim(s) *1-7, 18-25 and 27-30* is/are rejected.

7)☒ Claim(s) *12-17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6 and 7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 18-25 and 27-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "bulk material" in claim 7 is indefinite. Though clearly, a compound specified in one of claims 1 to 6 would be a "bulk material" if it were present in an amount on the order of 1 metric tonne, it is not clear where the delineation between "bulk" and "not bulk" lies. Perhaps most importantly, the patentability of a chemical compound cannot be based on the amount of that compound, thus claim does not provide for any patentable distinction over the claims from which it depends. Claim 7 is not viewed as being further limiting.

The term "highly pure" in claims 18-20 and 23-25 is a relative term which renders the claim indefinite. The term "highly pure" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The characterization of a compound as being "highly pure" may signify different purities to different persons of ordinary skill in the art in different settings, such as to the analytical chemist, forensic chemist, medicinal chemist or pharmacist.

Claims in which "highly pure" is recited as a limitation have been examined from the point of view that if there is a disclosure of the specified compound in the absence of any characterization explicitly stating said compound is impure, the limitation is met.

Claim 21, 22 and 27-30 provide for the use of the specified chemical compounds, but since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 21, 22 and 27-30 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claims 21, 22 and 27-30 have not been further examined on the merits.

Obviousness-type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent

and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-7 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over allowed claims 3 and 4 of copending Application No. 09/700,094 in view of the specification of 09/700,094.

Though claims 3 and 4 of U.S. serial no. 09/700,094 do not recite salts of the compounds specified in those claims, the specification of U.S. serial no. 09/700,094 makes it clear that salts of the compounds of claims 3 and 4 of that application are within the scope of the invention disclosed in that application. Example "bb" demonstrates hydrochloride salt formation of several species, while the specification (page no. 6 in the PCT publication on which 09/700,094 is based - WO 99/58478) teaches that the compounds disclosed in that application comprise salts thereof with physiologically acceptable organic and inorganic acids. Page no. 35 in the PCT publication again contemplates salts of the compounds disclosed therein with "physiologically acceptable acids." One of ordinary skill in the art, given the disclosure of U.S. serial no. 09/700,094, and claims 3 and 4 of U.S. serial no. 09/700,094 would at once envisage the compounds of claims 3 and 4 of U.S. serial no. 09/700,094 in the form of salts commonly employed in formulating pharmaceutical dosage forms of drugs

– hydrochloride, hydrobromide, sulfate, phosphate, tartrate, fumarate, maleate, citrate and aspartate.

This is a provisional obviousness-type double patenting rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 18 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 94/11337 (Johansson et al).

Compounds of instant claims 18 and 23 are disclosed on page 12, lines 15-28. The compound was recovered in the form of white crystals after recrystallization from diisopropyl ether. The identity of the compound was verified by N.M.R. and melting point. The compound is stable, as no decomposition was reported.

The compound in the aforementioned Example is pure (+) isomer, which in this case has the (R) configuration (tolterodine is the (+) isomer and has the (R) configuration). The (-) isomer is crystallized in lines 29-34 of page 12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 20 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 94/11337 (Johansson et al).

A compound having the molecular structure depicted in claim 20 or 25, in pure, crystalline form would have been obvious to one of ordinary skill in the art at the time the invention was made.

Compounds having the molecular structures depicted in instant claims 20 and 25 are known from the prior art. The compounds are stable, that is, they do not spontaneously decompose. Compounds having the molecular structures depicted in instant claims 20 and 25 have an established utility as antimuscarinic drugs in treatment of, for example, urinary incontinence.

Page 13, lines 16-30 discloses synthesis of a compound having the molecular structure depicted in claims 20 and 25 from the 2-benzyloxy substituted precursor. The compound is the (+) isomer, which corresponds to the (R) configuration for the particular compound (tolterodine is the (+) isomer and has the (R) configuration). The corresponding (-) isomer is synthesized in a similar manner on page 14, lines 6-11.

The Johansson et al publication teaches that free bases of the 3,3-diphenylproprylamines disclosed therein are suitable for pharmaceutical application. Page 6, lines 36-38 – page 7, lines 1-3 clearly state that free bases of any of the compounds of formula (I) disclosed in that publication are contemplated for pharmaceutical application. Thus, though the compound on page 13, lines 16-30 is converted to the mandelic acid salt, Johansson et al teaches that the free base, the form in which the compound was present initially, is suited for incorporation into

compositions for oral use, injection or nasal spray, and may be combined with materials so that it may be delivered enterally, percutaneously or parenterally.

A pharmacist or medicinal chemist of ordinary skill in the art, knows that free amines are more lipophilic than their corresponding salts, and therefore are suited for incorporation into dosage forms requiring a drug with lipophilic character such as a patch for percutaneous administration of the drug. Therefore, a crystallized form of the free base of a compound having the molecular structure depicted in instant claims 20 and 25 would be obvious to make. Doing so would be well within the skill of the average practitioner, and Johannson et al demonstrates crystallization of other free bases in the examples of WO 94/11337 (see above in *Claim Rejections – 35 USC* § 102). A crystalline form of the free base would be necessary for conveniently weighing and compounding the substance into a pharmaceutically elegant dosage form, such as a dosage form for percutaneous administration of the substance.

Claims 19 and 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/43242 (Johansson et al '942).

A compound having the molecular structure depicted in claim 19 and 24, in pure, crystalline form would have been obvious to one of ordinary skill in the art at the time the invention was made.

Johansson et al '942 discloses compounds having the molecular structures depicted in claims 19 and 24 on page 26 in Example 9 (the (R) isomer). The hydrochloride of this compound is prepared, however. Therefore the deficiency of

Johansson et al '942 with respect to claims 19 and 24 is that no example is present in Johansson et al '942 demonstrating crystallization of a free base of a compound having the molecular structure depicted in claims 19 and 24.

Johansson et al '942 expressly suggests that free bases, as well as the salts of compounds of formula I in that publication, are effective treatments for a disorder relating to urinary incontinence and may be incorporated into a variety of different types of dosage forms, including dosage forms for percutaneous administration of the compound (page 3, lines 16-21 and page 13, lines 6-25).

Page 7, lines 4 and 5, disclose N,N-diisopropyl-3-(2-hydroxy-5-methyloxycarbonylphenyl)-3-phenylpropanamine, and its (R) isomer. This compound is not a salt. The compound is apparently stable, as Johannson et al does not describe any difficulties in its synthesis (Example 9, referred to above), and teaches that the compound is preferred and suitable for incorporation into pharmaceutical compositions.

A pharmacist or medicinal chemist of ordinary skill in the art, knows that free amines are more lipophilic than their corresponding salts, and therefore are suited for incorporation into dosage forms requiring a drug with lipophilic character such as a patch for percutaneous administration of the drug. Therefore, a crystallized form of the free base of a compound having the molecular structure depicted in instant claims 19 and 24 would be obvious to make.

A crystalline form of the free base would be necessary for conveniently weighing and compounding the substance into a pharmaceutically elegant dosage form, such as a dosage form for percutaneous administration of the substance, but equally necessary

for any dosage form in which a free base of the active substance was to be compounded.

Cited of Interest

Pertinent to the compounds of claims 20 and 25 is Nilvebrant et al, "Antimuscarinic Potency and Bladder Selectivity of PNU-200577, a Major Metabolite of Tolterodine" Pharmacology and Toxicology. vol. 81, pages 169-172 (1997).

The Nilvebrant et al reference demonstrates the antimuscarinic potency of "PNU-200557," which has the molecular structure depicted in claims 20 and 25. The compound is employed as the mandelate salt in the experiments of that reference (page 170 – "Drugs and Chemicals").

Claim Objections/Allowable Subject Matter

Claims 3, 5-7, 21, 22 and 27-30, in addition to those claims being rejected for reasons set forth *supra*, are objected to for improper multiple dependency. A multiply dependent claim cannot simultaneously depend from more than one claim at a time. Claims 3, 5-7 have been examined on the merits in this Office action as though they were in proper multiply dependent form.

Claims 8-11 are allowed. The only disclosure of the compounds of formulae I or 2, as specified in claims 8 and 10, respectively, is in allowed U.S. patent application 09/700,094, over which the compounds of claims 1-7 were rejected for Obviousness-type Double Patenting, in WO 99/58478, which is the PCT application on which the U.S. application is based, and in the German patent application DE 98108608.5, which is the basis for WO 99/58478. The compounds of formulae I and 2 are made by a different

process in WO 99/58478 and US serial no. 09/700,094. In these disclosures, the methyl ester group is reduced first, followed by cleavage of the benzyloxy group. There is no suggestion to reverse these steps in WO 99/58478 and U.S. serial no. 09/700,094.

Claims 12-17 are objected to for being improper multiple dependent claims. A multiply dependent claim cannot simultaneously depend from more than one claim at a time. Claims 12-17 have been examined on the merits in this Office action as though they were in proper multiply dependent form. Claim 17 erroneously refers to isobutyryl chloride as "isobutyrate chloride." Isobutyryl chloride is recited in claim 15. Correction would be appreciated.

If amended so as to place them in proper form, claims 12-17 would be allowable.

Claim 26 is allowed. There is no disclosure of the compound of claim 26 in the prior art.

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (703) 305-2050. The examiner can normally be reached Monday-Friday from 7:00am to 3:30pm. If Attempts to reach the examiner are unsuccessful, the examiner's supervisor, Mukund Shah, can be reached at (703) 308-4716. The fax number for the organization where this application or proceeding is assigned is (703) 308-4556 for regular communications and (703) 308-4242 for after-final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

zt

Mukund Shah
Supervisory Patent Examiner
Art Unit 1624

Notice of References Cited	Application/Control No. 10/130,214	Applicant(s)/Patent Under Reexamination MEESE, CLAUS	
	Examiner Zachary C. Tucker	Art Unit 1624	Page 1 of 1

U.S. PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Name	Classification
	A	US-			
	B	US-			
	C	US-			
	D	US-			
	E	US-			
	F	US-			
	G	US-			
	H	US-			
	I	US-			
	J	US-			
	K	US-			
	L	US-			
	M	US-			

FOREIGN PATENT DOCUMENTS

*		Document Number Country Code-Number-Kind Code	Date MM-YYYY	Country	Name	Classification
	N					
	O					
	P					
	Q					
	R					
	S					
	T					

NON-PATENT DOCUMENTS

*		Include as applicable: Author, Title Date, Publisher, Edition or Volume, Pertinent Pages)
	U	Nilvebrant et al, "Antimuscarinic Potency and Bladder Selectivity of PNU-200577, a Major Metabolite of Tolterodine" Pharmacology and Toxicology. vol. 81, pages 169-172 (1997).
	V	
	W	
	X	

*A copy of this reference is not being furnished with this Office action. (See MPEP § 707.05(a).)
Dates in MM-YYYY format are publication dates. Classifications may be US or foreign.

PTO/-A820 (08-00)
Approved for use through 10/31/2002. OMB 0651-0031
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Information Disclosure Statement – PTO 1449 (Modified) Sheet 1 of 1

INFORMATION DISCLOSURES STATEMENT BY APPLICATION (use as many sheets as necessary)	Docket Number (Optional) 41946/32854	Application Number 10/130214
	Applicant Meese, Claus	
	Filing Date 5/14/2002	Group Art Unit ~~1614~~ 1624

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	REF	DOCUMENT NUMBER	ISSUE DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

	REF	DOCUMENT NUMBER	ISSUE DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
ZT		9 4 1 1 3 3 7	May 26, 1994	World Intellectual Property Organization	—	—		
ZT		9 8 4 3 9 4 2	October 8, 1998	World Intellectual Property Organization	—	—		

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

ZT		L. Palmer, L. Andersson, T. Andersson, U. Stenberg; *Determination of tolterodine and the 5-hydroxymethly metabolite in plasma, serum and urine using gas chromatography-mass spectrometry*; Journal of Pharmaceutical and Biomedical Analysis; January 20, 1997; Pages 155-165.

EXAMINER [signature] DATE CONSIDERED 30 JULY 2003

1952469

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Information Disclosure Statement – PTO 1449 (Modified)

Sheet 1 of 1

INFORMATION DISCLOSURES STATEMENT BY APPLICATION (use as many sheets as necessary)	Docket Number (Optional) 41946/32854	Application Number 10/130214
	Applicant Meese, Claus	
	Filing Date 5/14/2002	Group Art Unit ~~1614~~ 1624

U.S. PATENT DOCUMENTS

EXAMINER INITIAL	REF	DOCUMENT NUMBER	ISSUE DATE	NAME	CLASS	SUBCLASS	FILING DATE IF APPROPRIATE

FOREIGN PATENT DOCUMENTS

	REF	DOCUMENT NUMBER	ISSUE DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION YES	TRANSLATION NO
ZT		~~99~~ 99 ~~50~~ 83 ~~42~~ 71 ~~82~~	11/18/99	Patent Cooperation Treaty	—	—		

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, Etc.)

EXAMINER	DATE CONSIDERED
	30 JULY 2003

Burden Hour Statement: This form is estimated to take 2 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, Washington, DC 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Washington, DC 20231.

1952469

SEARCH TRANSCRIPT
10/130,214
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FILE 'HOME' ENTERED AT 09:11:02 ON 30 JUL 2003

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.21	0.21

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Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 28 JUL 2003 HIGHEST RN 556740-18-2
DICTIONARY FILE UPDATES: 28 JUL 2003 HIGHEST RN 556740-18-2

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2003

Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. See HELP PROPERTIES for more information. See STNote 27, Searching Properties in the CAS Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf

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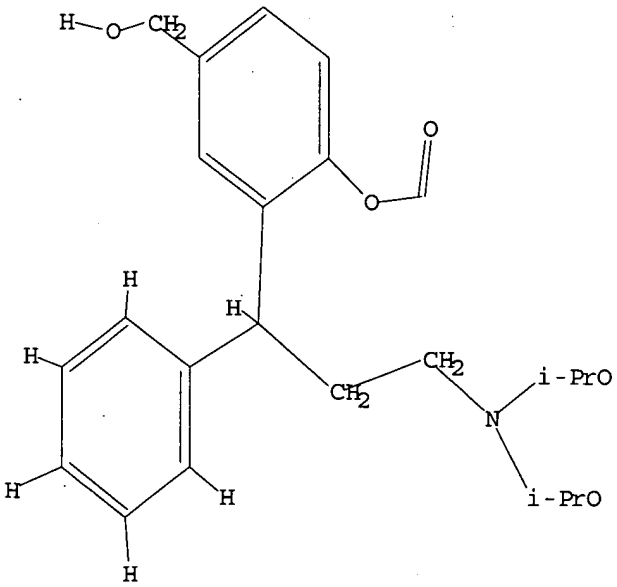

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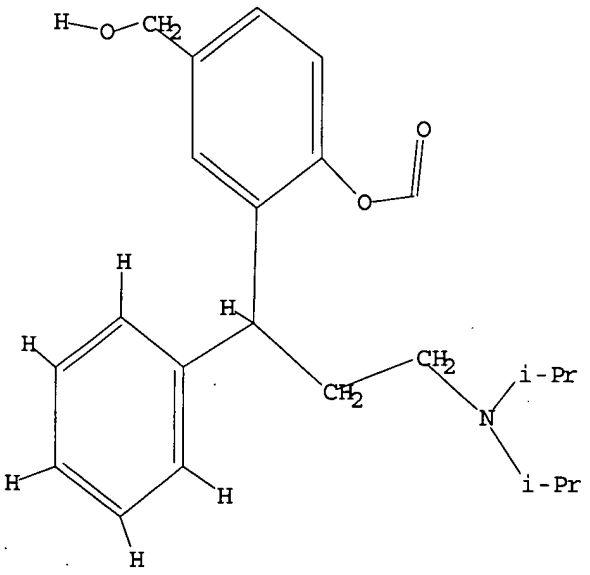

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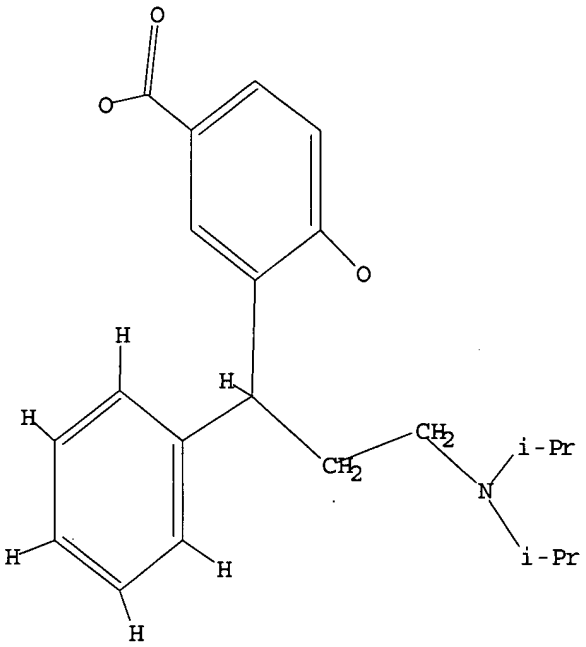

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FILE COVERS 1907 - 30 Jul 2003 VOL 139 ISS 5
FILE LAST UPDATED: 29 Jul 2003 (20030729/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

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            13 L8
L9          14 L6 OR L8

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L9 ANSWER 1 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER:	2003:335062 CAPLUS
DOCUMENT NUMBER:	138:353732
TITLE:	Quarternary ammonium compounds and their use as antimuscarinic agents
INVENTOR(S):	Richards, Ivan; Cammarata, Sue K.; Wegner, Craig D.; Hawley, Michael; Warchol, Mark P.; Kontny, Mark; Morozowich, Walter; Kolbasa, Karen P.; Moon, Malcolm W.; Bonafoux, Dominique; Wolfson, Sergey G.; Lennon, Patrick J.
PATENT ASSIGNEE(S):	Pharmacia & Upjohn Company, USA
SOURCE:	PCT Int. Appl., 69 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003035599	A1	20030501	WO 2002-US34529	20021025

W: 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, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR,

NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-348930P P 20011026
US 2002-361979P P 20020306
US 2002-391521P P 20020625

OTHER SOURCE(S): MARPAT 138:353732

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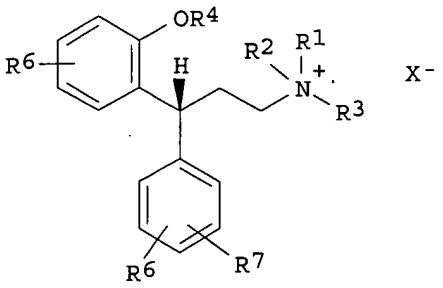


I

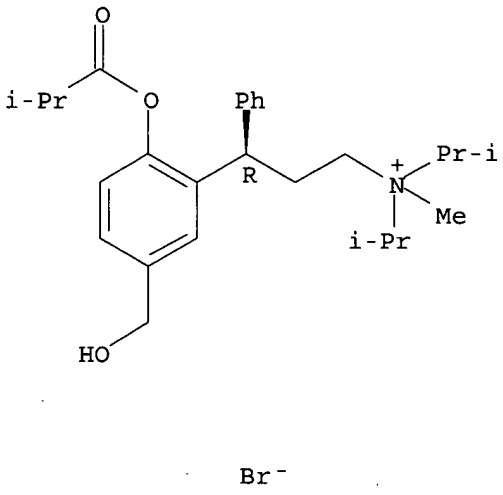
AB Novel quaternary ammonium compds. I [R1-R3 = (un)substituted alkyl; NR1R2, NR2R3, NR1R3 = heterocyclic; R4 = H, Me,acyl, alkoxycarbonyl, (un)substituted NH2; R5-R7 = H, OMe, OH, CONH2, SO2NH2, F, Cl, Br, I, CF3, (un)substituted alkyl; X = anion of a pharmaceutically acceptable acid] were prepd. for use as antimuscarinic agents. Thus, tolterodine tartrate was converted to the free base and quaternized with MeI to give (R)-5,2-Me(OH)C6H3CHPhCH2CH2N+(CHMe2)2Me I- which has high affinity, but little selectivity for M1-M5 muscarinic receptors.

IT **518360-93-5P**
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn.of diarylpropylammonium salts as antimuscarinic agents)

RN 518360-93-5 CAPLUS

CN Benzenepropanaminium, 5-(hydroxymethyl)-N-methyl-N,N-bis(1-methylethyl)-2-(2-methyl-1-oxopropoxy)-.gamma.-phenyl-, bromide, (.gamma.R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



Br-

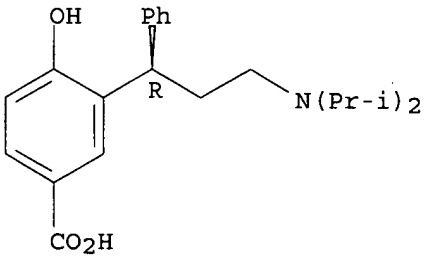
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 2 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:818306 CAPLUS
DOCUMENT NUMBER: 138:407019
TITLE: Sonic spray ionization interface for liquid chromatography-mass spectrometry
AUTHOR(S): Bjorkman, Helena T.; Edlund, Per-Olof; Jacobsson, Sven P.
CORPORATE SOURCE: Department of Analytical Chemistry, Stockholm University, Stockholm, SE-10691, Swed.
SOURCE: Analytica Chimica Acta (2002), 468(2), 263-274
CODEN: ACACAM; ISSN: 0003-2670
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A sonic spray ionization (SSI) interface for liq. chromatog.-mass spectrometry (LC-MS) anal. was optimized for anal. of 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-methyl-phenol (tolterodine), used as a model drug substance, and the influence of different parameter settings was evaluated using factorial design. A comparison between SSI and electrospray ionization (ESI) was made for tolterodine, tolterodine metabolites, and a set of steroids. SSI was found to give slightly poorer repeatability and broader peaks for tolterodine compared to ESI. However, there was no significant difference in chromatog. peak shape, and the repeatability using SSI was similar to that obtained using ESI if a ratio (area of tolterodine/area of metabolite) was used. In this study, the sensitivity was higher using SSI. For the anal. of pregnanolone, less water loss was obtained using SSI, probably due to less energy being transferred to the analyte upon ionization.

IT **194482-44-5**
RL: ANT (Analyte); ANST (Analytical study)
(sonic spray ionization interface for liq. chromatog.-mass spectrometry)
RN 194482-44-5 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 3 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:51413 CAPLUS
DOCUMENT NUMBER: 136:102178
TITLE: Preparation of 3,3-diarylpropylamines via hydroformylation-amination of diarylethenes in presence of a transition metal catalyst
INVENTOR(S): Donsbach, Martin; Eilbracht, Peter; Buss, Christian; Schmidt, Andreas
PATENT ASSIGNEE(S): Schwarz Pharma A.-G., Germany
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2

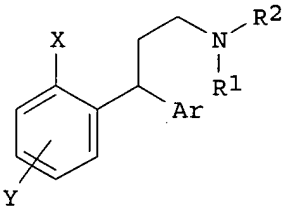
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002004399	A1	20020117	WO 2001-EP7803	20010706
W: 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, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 10033016	A1	20020124	DE 2000-10033016	20000707
EP 1299342	A1	20030409	EP 2001-962840	20010706
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: DE 2000-10033016 A 20000707
WO 2001-EP7803 W 20010706

OTHER SOURCE(S): CASREACT 136:102178; MARPAT 136:102178

GI



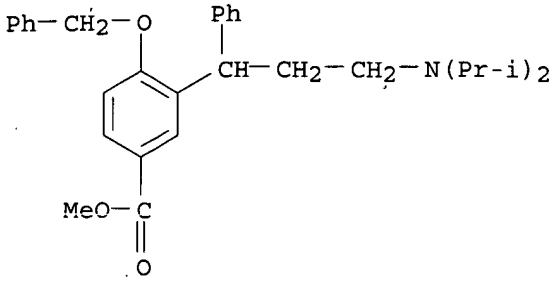
I

AB The invention relates to a novel method for producing 3,3-diarylpropylamines I [Ar = (un)substituted aryl; X = (un)substituted OH; Y = Cl, Br, I, CN, CH2OR, CHO, CO2H, CO2R; R = alkyl, aryl; R1, R2 = alkyl, cycloalkyl; NR1R2 = heterocyclic] by hydroformylation/hydrocarbonylation and subsequent reductive amination using a transition metal catalyst. Thus, 5,2-Me(HO)C6H3COPh was methylated and methylenated with MeP+Ph3 Br- to give 5,2-Me(MeO)C6H3CPh:CH2 which was treated with (Me2CH)2NH, CO, and H in presence of Rh(acac)(CO)2 and Bu3P to give 85% 5,2-Me(MeO)C6H3CHPhCH2CH2N(CHMe2)2.

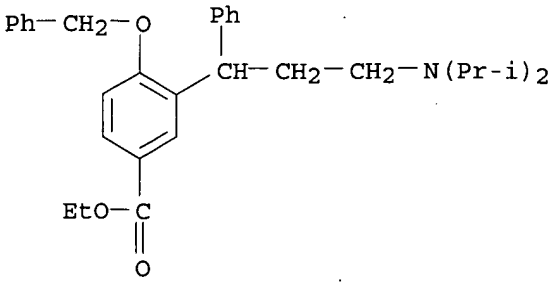
IT **286930-05-0P 389068-25-1P**
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of 3,3-diarylpropylamines via hydroformylation-amination of diarylethenes in presence of a transition metal catalyst)

RN 286930-05-0 CAPLUS

CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester (9CI) (CA INDEX NAME)



RN 389068-25-1 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, ethyl ester (9CI) (CA INDEX NAME)

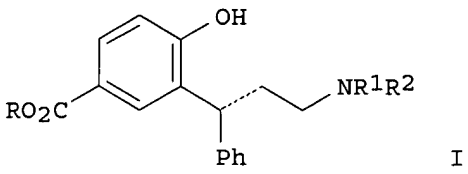


REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 4 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:923742 CAPLUS
DOCUMENT NUMBER: 136:37403
TITLE: Shortened synthesis of 3,3-diarylpropylamine derivatives
INVENTOR(S): Meese, Claus
PATENT ASSIGNEE(S): Schwarz Pharma A.-G., Germany
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001096279	A1	20011220	WO 2001-EP6577	20010611
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, 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, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
DE 10028443	C1	20020529	DE 2000-10028443	20000614
EP 1289929	A1	20030312	EP 2001-947355	20010611
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

NO 2002005967 A 20021212 NO 2002-5967 20021212
PRIORITY APPLN. INFO.: DE 2000-10028443 A 20000614
WO 2001-EP6577 W 20010611
OTHER SOURCE(S): CASREACT 136:37403; MARPAT 136:37403
GI



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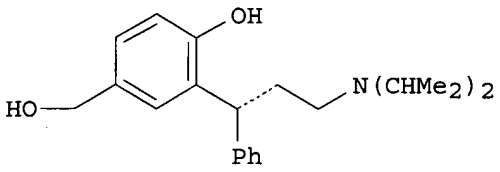
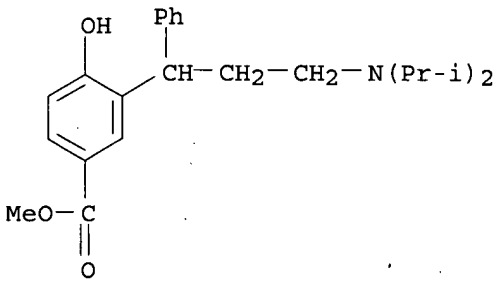


II

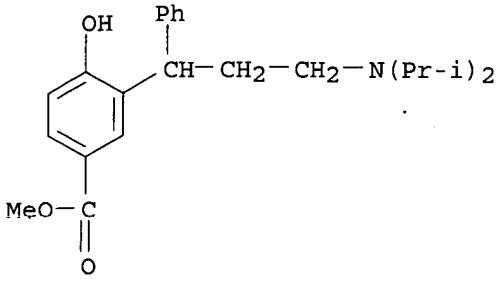
AB 3,3-Diarylpropylamines I [R = H, alkyl; R1, R2 = alkyl] are prepd. by reaction of RO2CC6H4OH-4 with PhCH:CHCO2H to give a 2-oxo-4-phenyl-3,4-dihydrobenzopyran-6-carboxylate which is resolved via its cinchonidine salt, the (R)-isomer hydrolyzed to the acid which is reesterified, reduced to the benzopyranol, and subjected to aminolysis to give I. I [R = Me, R1, R2 = CHMe2], thus obtained, was then reduced to the benzyl alc. II.

IT **214601-16-8P 380636-45-3P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(shortened synthesis of 3,3-diarylpropylamine derivs.)

RN 214601-16-8 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)



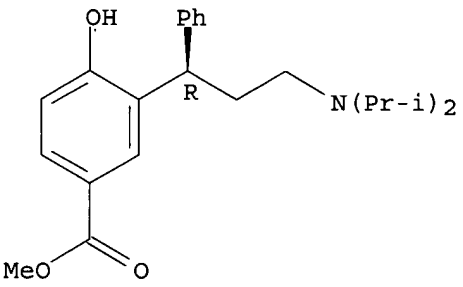
RN 380636-45-3 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester, hydrochloride (9CI) (CA INDEX NAME)



● HCl

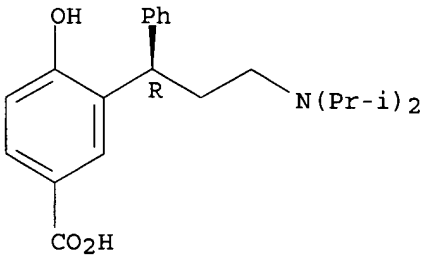
IT **214601-17-9P 380636-47-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(shortened synthesis of 3,3-diarylpropylamine derivs.)
RN 214601-17-9 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 380636-47-5 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



HCl

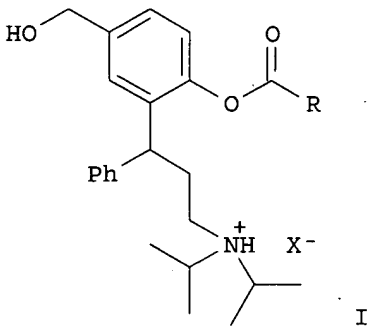
REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:449738 CAPLUS
DOCUMENT NUMBER: 135:61141
TITLE: Preparation of stable salts of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl esters.
INVENTOR(S): Meese, Claus
PATENT ASSIGNEE(S): Schwarz Pharma A.-G., Germany
SOURCE: Ger. Offen., 22 pp.
CODEN: GWXXBX
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PRIORITY APPLN ← APPLICANTS

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 19955190	A1	20010621	DE 1999-19955190	19991116
DE 29923134	U1	20000803	DE 1999-29923134	19991116
WO 2001035957	A1	20010525	WO 2000-EP11309	20001115
WO 2001035957	A3	20011227		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, 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, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
BR 2000015610	A	20020730	BR 2000-15610	20001115
EP 1230209	A2	20020814	EP 2000-989857	20001115
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2003514018	T2	20030415	JP 2001-537950	20001115
NO 2002002314	A	20020515	NO 2002-2314	20020515

PRIORITY APPLN. INFO.: DE 1999-19955190 IA 19991116
WO 2000-EP11309 W 20001115
OTHER SOURCE(S): MARPAT 135:61141
GI



I

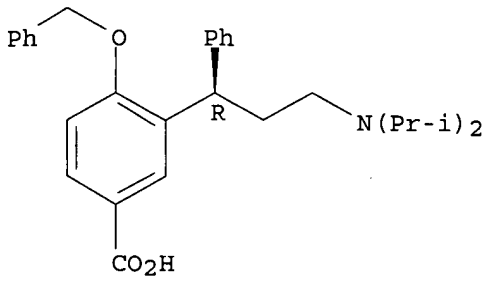
AB Title compds. [I; R = alkyl, cycloalkyl, (substituted) Ph; X- = residue of a physiol. acceptable (in)org. acid], were prepd. Thus, (R)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl isobutyrate (II) (prepn. given) in 2-butanone was treated with fumaric acid under warming to give 83.1% II.hydrogen fumarate.
IT **156755-33-8 286930-05-0**
RL: RCT (Reactant); RACT (Reactant or reagent)

(prepn. of stable salts of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl esters)

RN 156755-33-8 CAPLUS

CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, hydrochloride (9CI) (CA INDEX NAME)

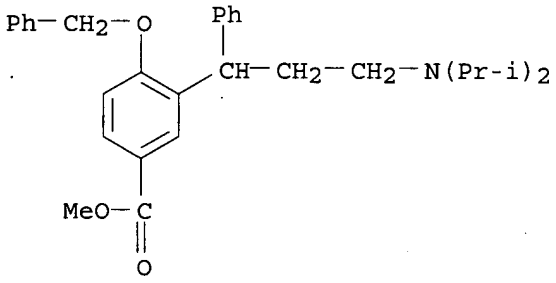
Absolute stereochemistry. Rotation (-).



● HCl

RN 286930-05-0 CAPLUS

CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester (9CI) (CA INDEX NAME)

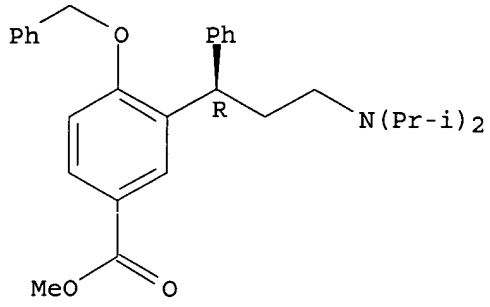


IT **156755-35-0P 214601-16-8P 214601-17-9P**
286930-02-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of stable salts of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl esters)

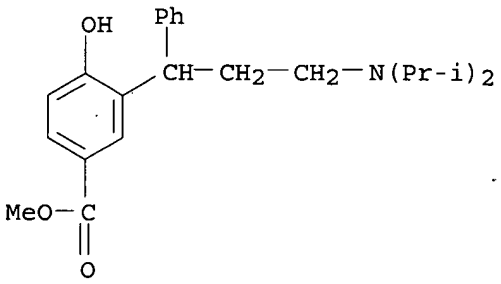
RN 156755-35-0 CAPLUS

CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

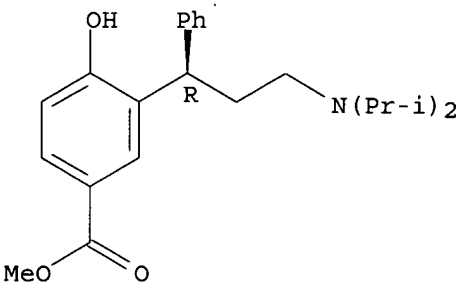


RN 214601-16-8 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)



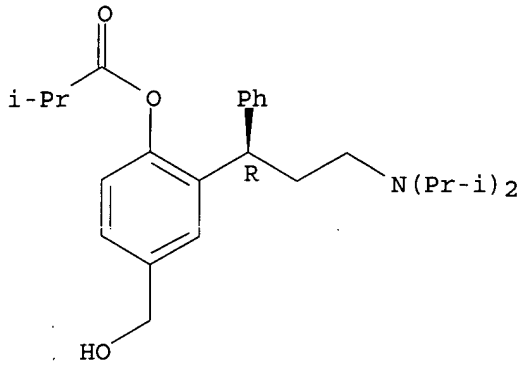
RN 214601-17-9 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 286930-02-7 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).

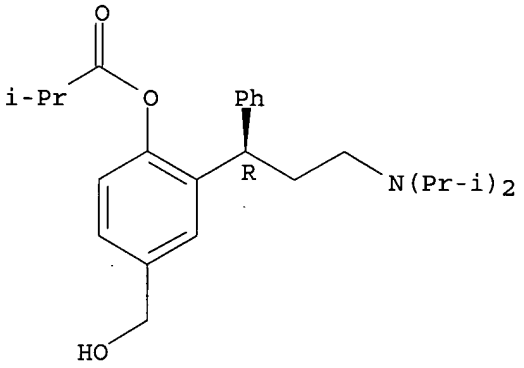


IT **286930-03-8P 345663-07-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of stable salts of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl esters)
RN 286930-03-8 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester, (2E)-2-butenedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 286930-02-7
CMF C26 H37 N O3

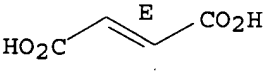
Absolute stereochemistry. Rotation (+).



CM 2

CRN 110-17-8
CMF C4 H4 O4

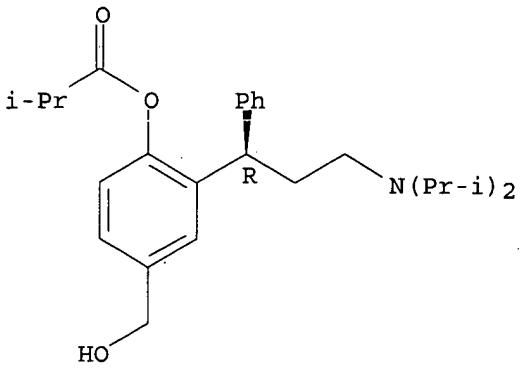
Double bond geometry as shown.



RN 345663-07-2 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester, hydrochloride (9CI) (CA

INDEX NAME)

Absolute stereochemistry. Rotation (+).

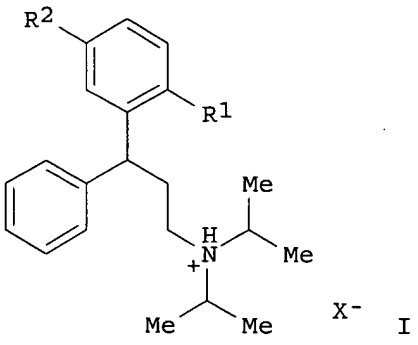


● HCl

L9 ANSWER 6 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:533448 CAPLUS
DOCUMENT NUMBER: 133:155419
TITLE: Stable salts of novel derivatives of 3,3-diphenylpropylamines
PATENT ASSIGNEE(S): Schwarz Pharma A.-G., Germany
SOURCE: Ger. Gebrauchsmusterschrift, 37 pp.
CODEN: GGXXFR
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 29923134	U1	20000803	DE 1999-29923134	19991116
DE 19955190	A1	20010621	DE 1999-19955190	19991116

PRIORITY APPLN. INFO.: DE 1999-19955190 IA 19991116 ← APPLICANTS F. P. APP'N
OTHER SOURCE(S): MARPAT 133:155419
GI



I

AB 3,3-Diphenylpropylamine salts I [R1 = RCO2; R = C1-6 alkyl, C3-10

cycloalkyl, (substituted) Ph; R2 = CH2OH; X = inorg. or org. acid] are prepd. for use as prodrugs of agents for treatment of urinary incontinence and other spasmogenic disorders. I show improved absorption through biol. membranes and improved metabolic patterns and are easily crystd. I are prepd. from I free base (R1 = PhCH2O, R2 = CO2Me) by debenzylation, redn., acylation, and combination with HX. Thus, R-(-)-I-HCl (R1 = PhCH2O, R2 = CO2H) was esterified by refluxing in acidic MeOH, the ester was reduced with LiAlH4, the resulting carbinol was reduced with Raney Ni/H2, and the product [R-(+)-I free base, R = CHMe2] was converted to its H fumarate salt by heating with equimolar fumaric acid in 2-butanone; the salt was crystd. by addn. of cyclohexanone and cooling to 0.degree..

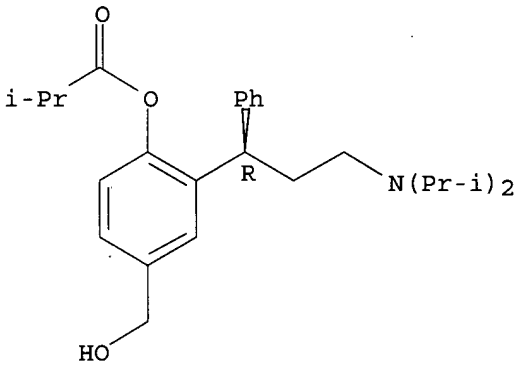
IT **286930-03-8P 286930-04-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(stable salts of novel derivs. of diphenylpropylamines)

RN 286930-03-8 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester, (2E)-2-butenedioate (1:1) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 286930-02-7
CMF C26 H37 N O3

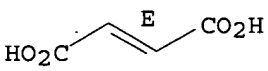
Absolute stereochemistry. Rotation (+).



CM 2

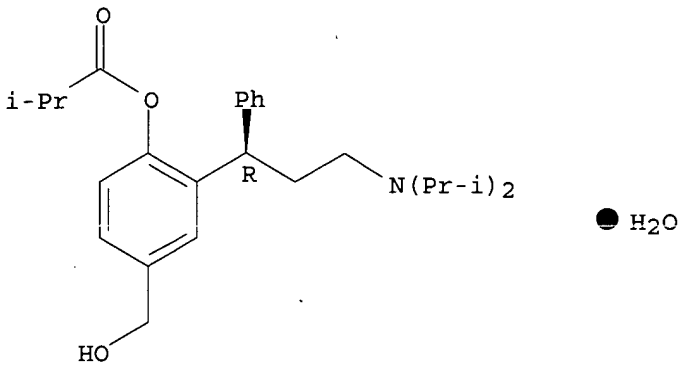
CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.



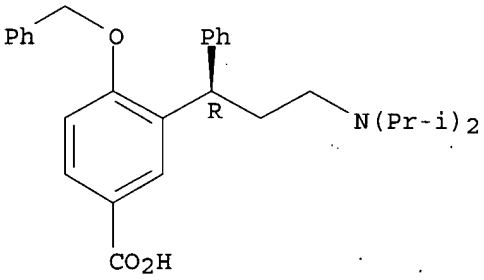
RN 286930-04-9 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester, hydrochloride, monohydrate (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



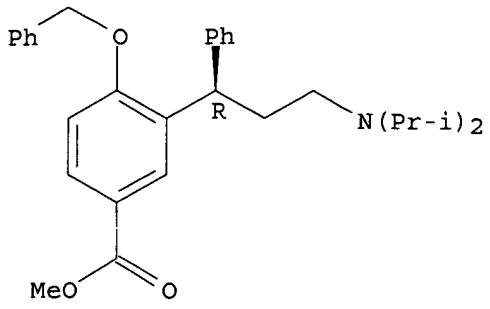
IT **156755-33-8**
RL: RCT (Reactant); RACT (Reactant or reagent)
(stable salts of novel derivs. of diphenylpropylamines)
RN 156755-33-8 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

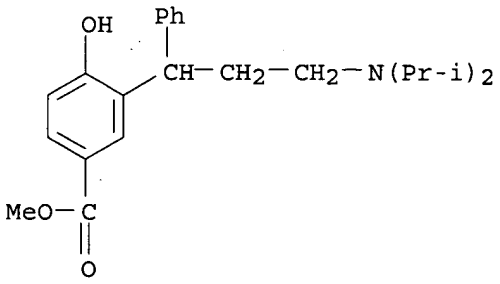


IT **156755-35-0P 214601-16-8P 214601-17-9P**
286930-05-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(stable salts of novel derivs. of diphenylpropylamines)
RN 156755-35-0 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

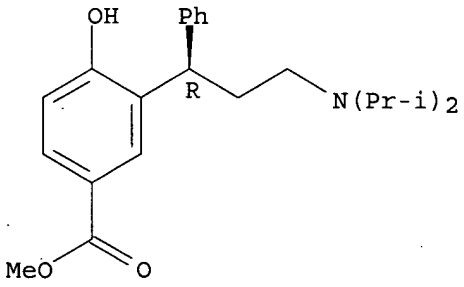


RN 214601-16-8 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)

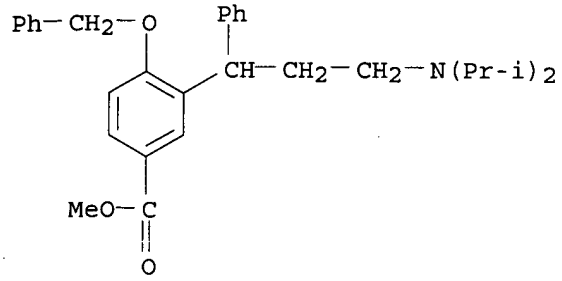


RN 214601-17-9 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 286930-05-0 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester (9CI) (CA INDEX NAME)



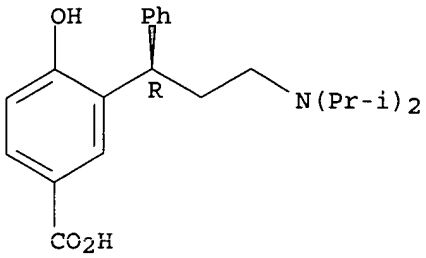
L9 ANSWER 7 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:779638 CAPLUS
DOCUMENT NUMBER: 132:202559
TITLE: Capillary solid-phase extraction-tandem mass spectrometry for fast quantification of free concentrations of tolterodine and two metabolites in ultrafiltered plasma samples
AUTHOR(S): Swart, R.; Koivisto, P.; Markides, K. E.
CORPORATE SOURCE: Institute of Chemistry, Department of Analytical Chemistry, Uppsala University, Uppsala, 751 21, Swed.
SOURCE: Journal of Chromatography, B: Biomedical Sciences and Applications (1999), 736(1 + 2), 247-253
CODEN: JCBBEP; ISSN: 0378-4347
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A capillary solid-phase extn. (SPE) system has been coupled directly to electrospray tandem mass spectrometry for quantification of free tolterodine and metabolite concns. in plasma. The unbound fraction of these compds. was obtained by ultrafiltration of plasma. The ultrafiltrate was directly injected onto the SPE capillary (4 mm.times.200 .mu.m, 5 .mu.m C18). After desalting and clean-up of the sample, the analytes were eluted in backflush mode with methanol-1 mM triethylamine (70:30, vol./vol.), providing considerable solute focusing. Elution from the SPE capillary was improved by inserting a short trapping capillary between the SPE capillary and the MS interface, by which analyte focusing was increased. The unresolved compds. eluted simultaneously with the remaining matrix compds. and were detected in a multiple-reaction monitoring (MRM) mode. No interference of the sample matrix on detection was obsd., allowing aq. stds. to be used for calibration. Linear calibration curves were obtained between 0.05 and 1000 ng/mL (corresponding to 150 pM-3 .mu.M) and the limit of detection was 50 pg/mL injecting 10 .mu.l. Equilibration of the SPE capillary, sample loading, elution and detection took less then 6 min per sample.

IT **194482-44-5**
RL: ANT (Analyte); ANST (Analytical study)
(capillary solid-phase extn.-tandem mass spectrometry for fast quantification of free concns. of tolterodine and two metabolites in ultrafiltered plasma samples)

RN 194482-44-5 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:736261 CAPLUS
DOCUMENT NUMBER: 131:336818
TITLE: Preparation of 3,3-diphenylpropylamines as antimuscarinic agents.
INVENTOR(S): Sparf, Bengt; Meese, Claus O.
PATENT ASSIGNEE(S): Schwarz Pharma AG, Germany
SOURCE: Eur. Pat. Appl., 27 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 957073	A1	19991117	EP 1998-108608	19980512
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
CA 2328920	AA	19991118	CA 1999-2328920	19990511
WO 9958478	A1	19991118	WO 1999-EP3212	19990511
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, 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, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9941412	A1	19991129	AU 1999-41412	19990511
AU 748057	B2	20020530		
BR 9910406	A	20010109	BR 1999-10406	19990511
EP 1077912	A1	20010228	EP 1999-924929	19990511
EP 1077912	B1	20020703		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AT 220056	E	20020715	AT 1999-924929	19990511
EP 1254890	A1	20021106	EP 2002-13481	19990511
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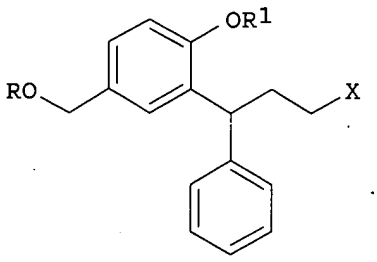
NZ 507487	A	20021126	NZ 1999-507487	19990511
ES 2181443	T3	20030216	ES 1999-924929	19990511
RU 2199525	C2	20030227	RU 2000-125813	19990511
JP 2003519079	T2	20030617	JP 2000-548284	19990511
NO 2000005669	A	20010111	NO 2000-5669	20001110

PRIORITY APPLN. INFO.:
EP 1998-108608 A 19980512
EP 1999-924929 A3 19990511
WO 1999-EP3212 W 19990511

OTHER SOURCE(S): MARPAT 131:336818
GI

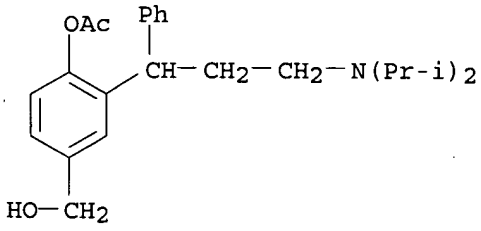


I

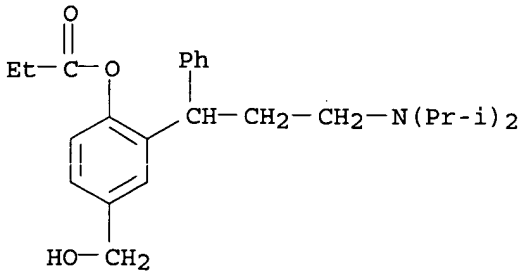
AB Title compds. (I; R = H, Me, Et, Pr, Me2CH, Bu, iso-Bu, pentyl, hexyl, PhCH2, alkyl, CHO, Ac, propionyl, isobutyryl, aminocarbonyl, aminosulfonyl, MeO2C, etc.; R1 = H, Me, Et, Pr, Me2CH, Bu, iso-Bu, pentyl, hexyl, PhCH2, alkyl, phenylalkyl; Z = NR8R9; R8, R9 = hydrocarbyl; NR8R9 = atoms to form a ring; with a proviso), were prepd. as antimuscarinic agents (no data). Thus, 4-bromophenol, cinnamoyl chloride, and Et3N were stirred 18 h in CH2Cl2 to give 99.8% 3-phenylacrylic acid 4-bromophenyl ester. This was refluxed 2 h with HOAc/H2SO4 to give 43.8% 6-bromo-4-phenylchroman-2-one. The latter was refluxed with benzyl bromide, K2CO3, and NaI in acetone/MeOH to give 102.1% crude Me 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionate, which was stirred with LiAlH4 in THF to give 96.3% 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol. This was stirred with tosyl chloride and pyridine in CH2Cl2 for 18 h to give 93.6% tosylate ester, which was refluxed 97 h with diisopropylamine in MeCN to give 77.9% [3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl]diisopropylamine. The latter was converted in several steps to 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol, which was acylated to give I.

IT **250214-41-6P 250214-42-7P 250214-43-8P**
250214-44-9P 250214-45-0P 250214-46-1P
250214-47-2P 250214-48-3P 250214-49-4P
250214-50-7P 250214-88-1P 250214-89-2P
250214-91-6P 250214-92-7P 250214-94-9P
250214-96-1P 250215-02-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of 3,3-diphenylpropylamines as antimuscarinic agents)

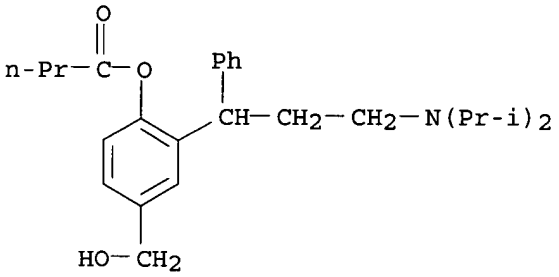
RN 250214-41-6 CAPLUS
CN Benzenemethanol, 4-(acetyloxy)-3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]- (9CI) (CA INDEX NAME)



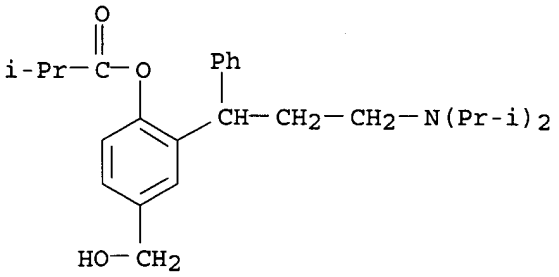
RN 250214-42-7 CAPLUS
CN Benzenemethanol, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(1-oxopropoxy)- (9CI) (CA INDEX NAME)



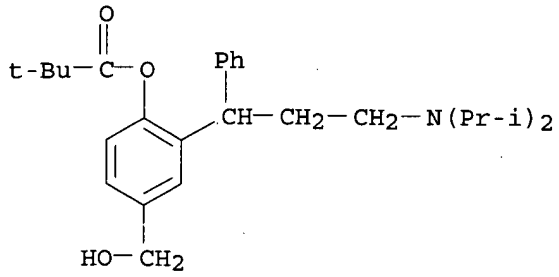
RN 250214-43-8 CAPLUS
CN Butanoic acid, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (9CI) (CA INDEX NAME)



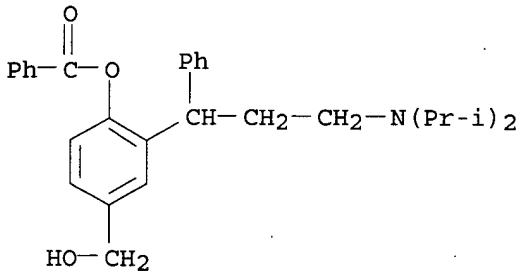
RN 250214-44-9 CAPLUS
CN Propanoic acid, 2-methyl-, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (9CI) (CA INDEX NAME)



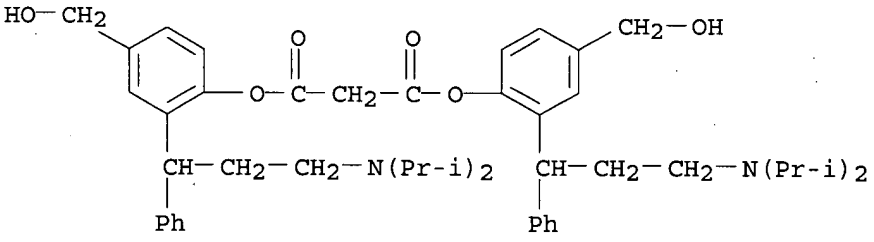
RN 250214-45-0 CAPLUS
CN Propanoic acid, 2,2-dimethyl-, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (9CI) (CA INDEX NAME)



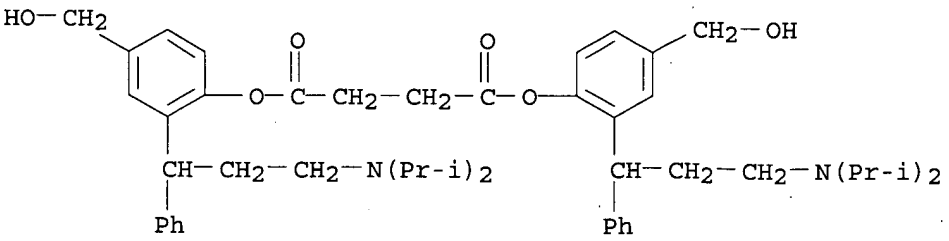
RN 250214-46-1 CAPLUS
CN Benzenemethanol, 4-(benzoyloxy)-3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]- (9CI) (CA INDEX NAME)



RN 250214-47-2 CAPLUS
CN Propanedioic acid, bis[2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl] ester (9CI) (CA INDEX NAME)

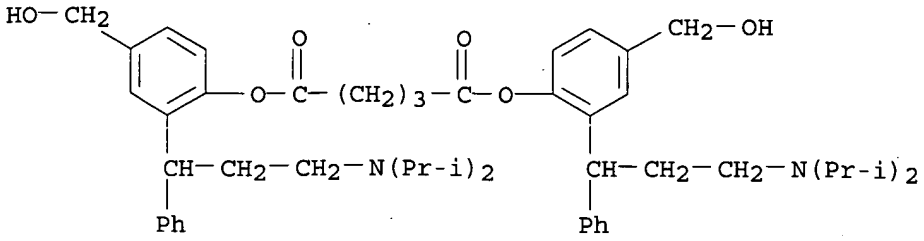


RN 250214-48-3 CAPLUS
CN Butanedioic acid, bis[2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl] ester (9CI) (CA INDEX NAME)

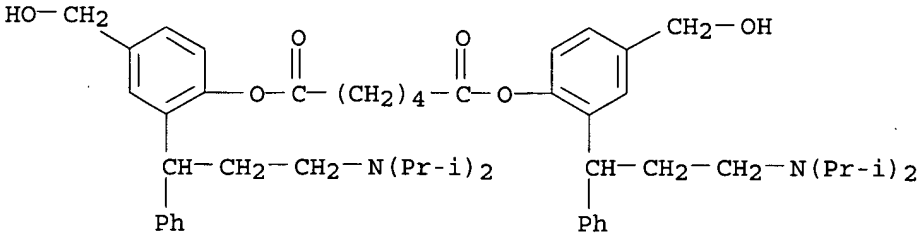


RN 250214-49-4 CAPLUS

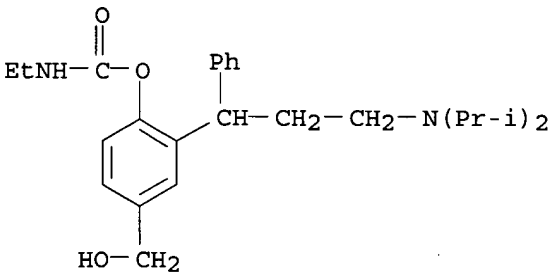
CN Pentanedioic acid, bis[2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl] ester (9CI) (CA INDEX NAME)



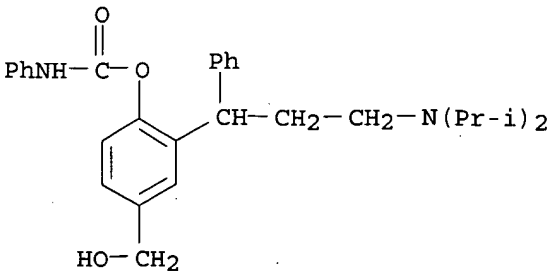
RN 250214-50-7 CAPLUS
CN Hexanedioic acid, bis[2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl] ester (9CI) (CA INDEX NAME)

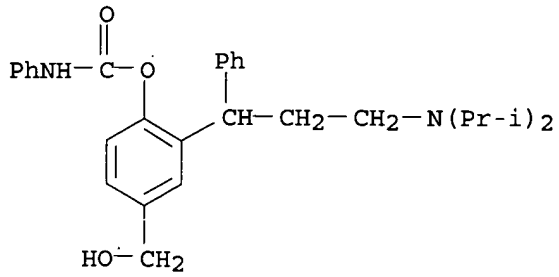


RN 250214-88-1 CAPLUS
CN Carbamic acid, ethyl-, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester (9CI) (CA INDEX NAME)

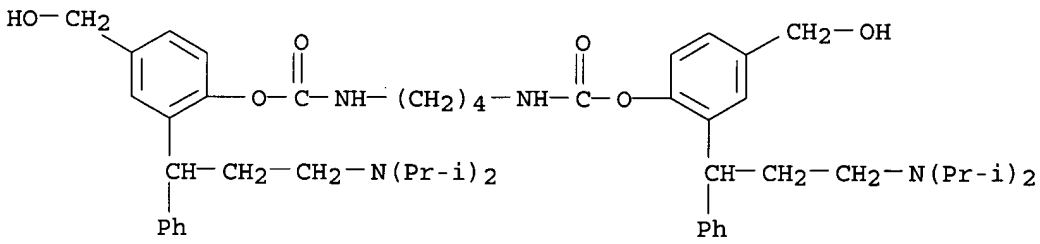


RN 250214-89-2 CAPLUS
CN Benzenemethanol, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-[[(phenylamino)carbonyl]oxy]- (9CI) (CA INDEX NAME)

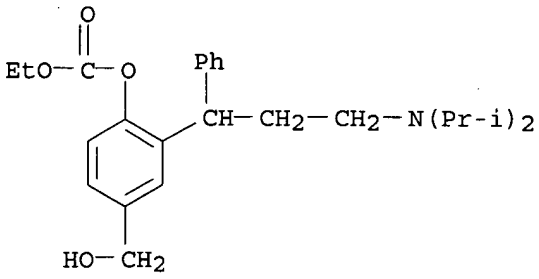




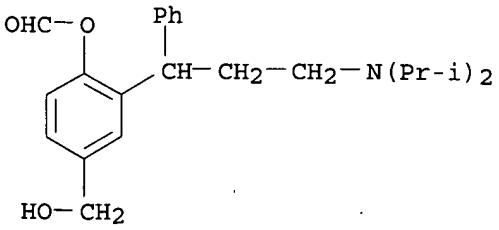
RN 250214-91-6 CAPLUS
CN Carbamic acid, 1,4-butanediylbis-, bis[2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl] ester (9CI) (CA INDEX NAME)



RN 250214-92-7 CAPLUS
CN Carbonic acid, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ethyl ester (9CI) (CA INDEX NAME)

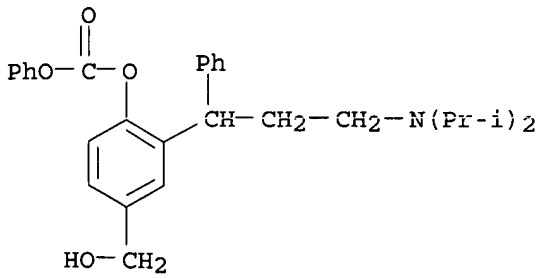


RN 250214-94-9 CAPLUS
CN Benzenemethanol, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(formyloxy)- (9CI) (CA INDEX NAME)

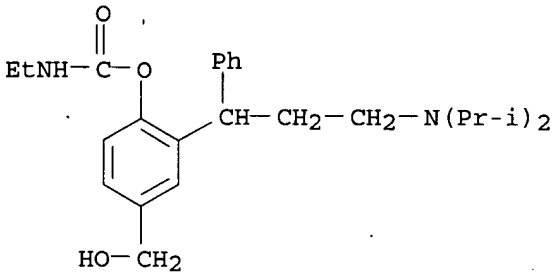


RN 250214-96-1 CAPLUS

CN Carbonic acid, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl phenyl ester (9CI) (CA INDEX NAME)

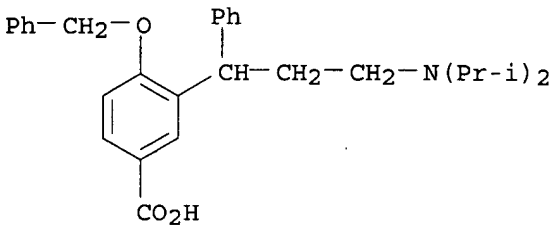


RN 250215-02-2 CAPLUS
CN Carbamic acid, ethyl-, 2-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(hydroxymethyl)phenyl ester, monohydrochloride (9CI) (CA INDEX NAME)



● HCl

IT **250214-38-1P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. of 3,3-diphenylpropylamines as antimuscarinic agents)
RN 250214-38-1 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, hydrochloride (9CI) (CA INDEX NAME)



HCl

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS

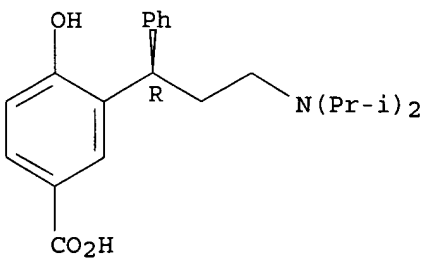
L9 ANSWER 9 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:692703 CAPLUS
DOCUMENT NUMBER: 132:87770
TITLE: Ketoconazole inhibits the metabolism of tolterodine in subjects with deficient CYP2D6 activity
AUTHOR(S): Brynne, N.; Forslund, C.; Hallen, B.; Gustafsson, L. L.; Bertilsson, L.
CORPORATE SOURCE: Department of Clinical Pharmacology, Pharmacia and Upjohn AB, Stockholm, SE-112 87, Swed.
SOURCE: British Journal of Clinical Pharmacology (1999), 48(4), 564-572
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The pharmacokinetics and safety of tolterodine and tolterodine metabolites was studied after single-and multiple-dose administration in the absence and presence of ketoconazole, an inhibitor of cytochrome P 450 (CYP) 3A4, in healthy volunteers with deficient CYP2D6 activity, i.e. poor metabolizers of debrisoquine. Eight healthy volunteers received single oral doses (2 mg) of tolterodine L-tartrate. Following a wash-out period of about 3 mo, six of the subjects participated in a multiple-dose (1 mg twice daily) phase of the study. Ketoconazole 200 mg was given once daily for 4-4.5 days during both the single and multiple dose tolterodine administration phases. Blood samples were drawn and the pharmacokinetics of tolterodine and its metabolites were detd. A decrease ($P < 0.01$) in apparent oral clearance of tolterodine, from 10-12 l h-1 to 4.3-4.7 l h-1, was obtained during concomitant administration of ketoconazole, yielding at least a two-fold increase in the area under the serum concn.-time curve after single as well as after multiple doses following single dose administration of tolterodine. The mean (.+-.s.d.) terminal half-life increased by 50% from 9.7.+-.2.7 h to 15.+-.5.4 h in the presence of ketoconazole. CYP3A4 is the major enzyme involved in the elimination of tolterodine in individuals with deficient CYP2D6 activity (poor metabolizers), since oral clearance of tolterodine decreased by 60% during ketoconazole coadministration. This inhibition resulted in 2.1-fold increase in AUC.

IT **194482-44-5**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(as tolterodine metabolite, ketoconazole inhibits the metab. of tolterodine in human subjects with deficient CYP2D6 activity)

RN 194482-44-5 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

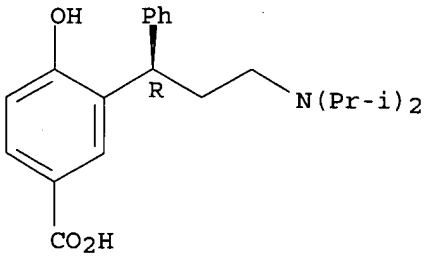
L9 ANSWER 10 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:692702 CAPLUS
DOCUMENT NUMBER: 132:87769
TITLE: Fluoxetine inhibits the metabolism of tolterodine-pharmacokinetic implications and proposed clinical relevance
AUTHOR(S): Brynne, N.; Svanstrom, C.; Aberg-Wistedt, A.; Hallen, B.; Bertilsson, L.
CORPORATE SOURCE: Departments of Clinical Pharmacology, Pharmacia and Upjohn AB, Stockholm, SE-112 87, Swed.
SOURCE: British Journal of Clinical Pharmacology (1999), 48(4), 553-563
CODEN: BCPHBM; ISSN: 0306-5251
PUBLISHER: Blackwell Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The change in disposition of tolterodine during coadministration of the potent cytochrome P 450 2D6 (CYP2D6) inhibitor fluoxetine was studied. Thirteen patients received tolterodine L-tartrate 2 mg twice daily for 2.5 days, followed by fluoxetine 20 mg once daily for 3 wk and then concomitant administration for an addnl. 2.5 days. They were characterized as extensive metabolizers (EM1 with one functional CYP2D6 gene, EM2 with two functional genes) or poor metabolizers (PM). Nine patients, three EM2 and four EM1 and two PM, completed the trial. Following tolterodine administration, the area under the serum concn.-time curve (AUC) of tolterodine was 4.4-times and 30-times higher among EM1 and PM, resp., compared with EM2. The AUC of the 5-hydroxymethyl metabolite (5-HM) was not quantifiable in PM. Fluoxetine significantly decreased ($P < 0.002$) the oral clearance of tolterodine by 93% in EM2 and by 80% in EM1. The AUC of 5-HM increased in EM2 and decreased in EM1. However, the exposure to the active moiety (unbound tolterodine +5-HM) was not significantly increased in the two phenotypes. The subdivision of the EM group showed a 2.1-fold increase in active moiety in EM2 but the exposure was still similar to EM1 compared with before the interaction. The study suggests a difference in the pharmacokinetics of tolterodine and its 5-hydroxymethyl metabolite depending on the no. of functional CYP2D6 genes. Fluoxetine significantly inhibited the hydroxylation of tolterodine. Despite the effect on the pharmacokinetics of tolterodine in extensive metabolizers, the clin. effect is expected to be within normal variation.

IT **194482-44-5**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(fluoxetine inhibits the metab. of tolterodine-pharmacokinetics)

RN 194482-44-5 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



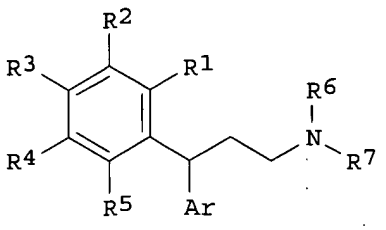
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS

RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

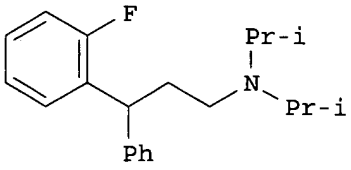
L9 ANSWER 11 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:682217 CAPLUS
DOCUMENT NUMBER: 129:316029
TITLE: Novel 3-aryl-3-phenylpropanamines with anticholinergic activity, their use in the treatment of urinary incontinence, and their preparation
INVENTOR(S): Johansson, Rolf; Haraldsson, Martin; Ringberg, Erik; Vagberg, Jan; Beierlein, Katarina; Emond, Rikard; Sjoberg, Birger
PATENT ASSIGNEE(S): Pharmacia and Upjohn AB, Swed.
SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9843942	A1	19981008	WO 1998-SE556	19980326
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9802478	A	19981008	ZA 1998-2478	19980324
AU 9867552	A1	19981022	AU 1998-67552	19980326
AU 739186	B2	20011004		
BR 9808069	A	20000308	BR 1998-8069	19980326
EP 1019358	A1	20000719	EP 1998-912864	19980326
EP 1019358	B1	20030507		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2001522355	T2	20011113	JP 1998-541548	19980326
AT 239693	E	20030515	AT 1998-912864	19980326
NO 9904438	A	19991126	NO 1999-4438	19990913
MX 9908862	A	20000228	MX 1999-8862	19990927
US 6313132	B1	20011106	US 1999-381868	19990927

PRIORITY APPLN. INFO.: SE 1997-1144 A 19970327
WO 1998-SE556 W 19980326
OTHER SOURCE(S): MARPAT 129:316029
GI



I



II

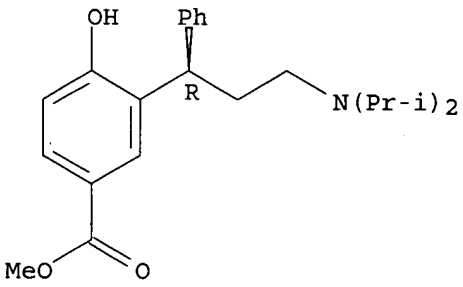
AB The invention relates to novel compds. I [wherein R1 = H, OH, alkyl, alkoxy, CF3, amino, alkanoylamino, alkanoyloxy, halo, hydroxyalkyl; R2, R3 = H, OH, alkyl, alkoxy, hydroxyalkyl, halo, carbamoyl, etc.; R4 =

(un)substituted alkyl or amino, CHO, CO2H, NO2, cyano, N3, alkoxy, and may also be H, Me, OMe, etc. under some circumstances; R5 = H, halo, alkyl; Ar = (un)substituted (hetero)aryl; R6, R7 = hydrocarbyl with optional OH groups or O bridge(s), and may form a ring; with several provisos], their salts with physiol. acceptable acids, their racemic mixts., and the individual enantiomers. The compds. have anticholinergic activity, and in particular are of use in the treatment of urinary incontinence. Sixty synthetic examples are given, and approx. 90 compds. (including free bases and salts) were prepd. and/or claimed. For instance, Wittig-type reaction of (EtO)2P(O)CH2CON(Pr-iso)2 with 2-fluorobenzophenone, followed by hydrogenation of the formed olefin and redn. of the amide with LiAlH4, gave after acidification, title compd. II.HCl. In a test for inhibition of carbachol-induced contraction of isolated guinea pig bladder strips, II had a KB value of 10 nM, and other compds. had values ranging from 1.18 nM to 3315 nM.

IT **214600-45-0P 214601-16-8P 214601-17-9P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of arylphenylpropanamines as anticholinergic agents)

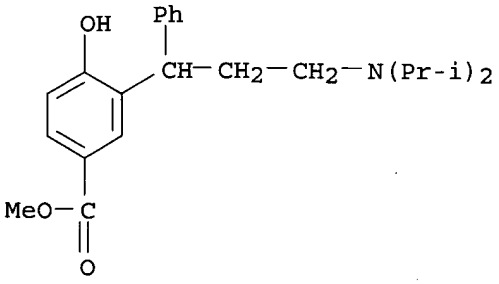
RN 214600-45-0 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester, hydrochloride (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



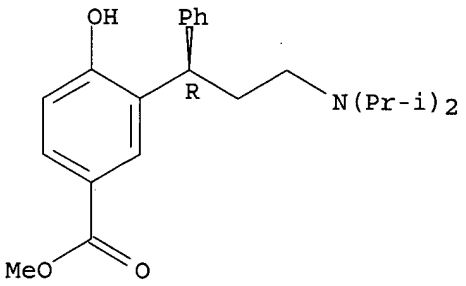
O HCl

RN 214601-16-8 CAPLUS
CN Benzoic acid, 3-[3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)



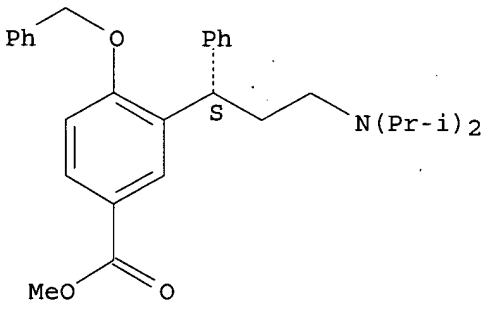
RN 214601-17-9 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT **156755-34-9**
RL: RCT (Reactant); RACT (Reactant or reagent)
(starting material; prepn. of arylphenylpropanamines as anticholinergic agents)
RN 156755-34-9 CAPLUS
CN Benzoic acid, 3-[(1S)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

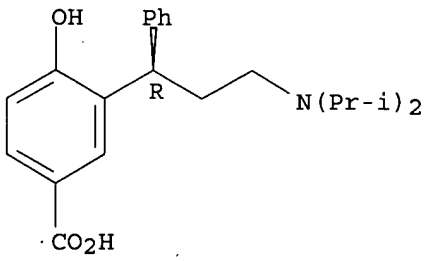
L9 ANSWER 12 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1998:393013 CAPLUS
DOCUMENT NUMBER: 129:156415
TITLE: Biotransformation of tolterodine, a new muscarinic receptor antagonist, in mice, rats, and dogs
AUTHOR(S): Andersson, Stig H. G.; Lindgren, Anders; Postlind, Hans
CORPORATE SOURCE: Department of Drug Metabolism, Pharmacia & Upjohn AB, Uppsala, S-751 82, Swed.
SOURCE: Drug Metabolism and Disposition (1998), 26(6), 528-535
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tolterodine is intended for the treatment of urinary urge incontinence and other symptoms assocd. with an overactive bladder. The in vivo metab. of 14C-labeled tolterodine was investigated in rats, mice, and dogs by anal. of blood and urine samples, whereas in vitro metab. studies were performed by incubation of [14C]tolterodine with mouse, rat, dog, and human liver microsomes in the presence of NADPH. Tolterodine was extensively metabolized in vivo. Mice and dogs showed similar metabolite patterns,

which correlated well with that obsd. in humans. In these species, tolterodine was metabolized along 2 different pathways, with the more important being the stepwise oxidn. of the 5-Me group to yield the 5-hydroxymethyl metabolite of tolterodine and then, via the aldehyde, the 5-carboxylic acid metabolite. The other pathway involved dealkylation of the nitrogen. In the subsequent phase II metab., tolterodine and the metabolites were conjugated with glucuronic acid to various degrees. Rats had a more extensive metab. and a markedly different metabolite pattern, with metabolites also being formed by hydroxylation of the nonsubstituted benzene ring. Gender differences were also obsd., with male rats showing more extensive metab. than females. Incubation of [14C]tolterodine yielded 5 metabolites with rat microsomes and 3 metabolites with mouse, dog, and human microsomes. The 5-hydroxymethyl metabolite of tolterodine and N-dealkylated tolterodine were major metabolites in all incubations, representing 83-99% of total metab. Although the extent of metab. varied among the species, the metabolic profiles were similar. Rat liver microsomes also formed metabolites hydroxylated in the nonsubstituted benzene ring. Thus, the metab. of tolterodine in mice and dogs corresponds to that obsd. in humans, whereas rats have a different metabolite pattern.

IT **194482-44-5**, PNU 200579 **210573-53-8**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(tolterodine biotransformation in mice, rats, dogs and humans)

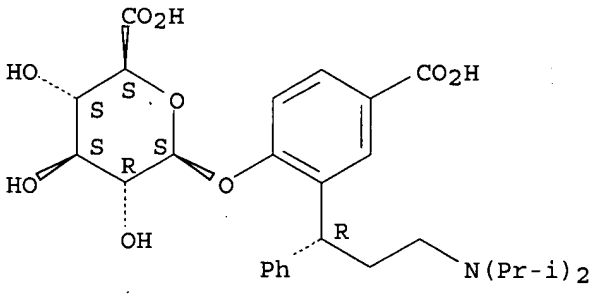
RN 194482-44-5 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 210573-53-8 CAPLUS
CN .beta.-D-Glucopyranosiduronic acid, 2-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-carboxyphenyl (9CI) (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

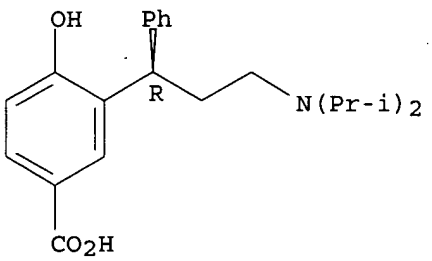
L9 ANSWER 13 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1997:478930 CAPLUS
DOCUMENT NUMBER: 127:199591
TITLE: Pharmacokinetics and pharmacodynamics of tolterodine in man. A new drug for the treatment of urinary bladder overactivity
AUTHOR(S): Brynne, N.; Stahl, M. M. S.; Hallen, B.; Edlund, P. O.; Palmer, L.; Hoglund, P.; Gabrielsson, J.
CORPORATE SOURCE: Department Clinical Pharmacology, Pharmacia and Upjohn AB, Uppsala, S-75182, Swed.
SOURCE: International Journal of Clinical Pharmacology and Therapeutics (1997), 35(7), 287-295
CODEN: ICTHEK; ISSN: 0946-1965
PUBLISHER: Dustri-Verlag Dr. Karl Feistle
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The pharmacokinetics, pharmacodynamics, and safety of tolterodine was detd. following single oral and i.v. doses in healthy volunteers. Major urinary metabolites were identified and mass balance was detd. Single oral doses of 0.2, 0.4, 0.8, 1.6, 3.2, 6.4, and 12.8 mg of tolterodine (as the tartrate salt) were given to 17 healthy male volunteers. Two i.v. doses (0.64, 1.28 mg) were administered to 8 of the volunteers and mass balance was studied after a single oral dose of 5 mg (14C)-tolterodine in 6 subjects. Tolterodine was rapidly absorbed following oral administration. The abs. bioavailability was highly variable, ranging from 10-70%. The vol. of distribution at steady-state ranged from 0.9-1.6 L/kg and systemic clearance ranged from 0.23-0.52 L/h/kg, which resulted in a terminal half-life of 2-3 h. Tolterodine exhibited high first-pass metab. and 2 hepatic metabolic pathways were identified: oxidn. and dealkylation. Independent of route of administration, < 1% of the parent compd. was excreted unchanged in urine. Five metabolites were structurally identified in urine. Following oral administration of (14C)-tolterodine, the excretion of radioactivity into urine and feces was 77 and 17%, resp. Tolterodine decreased stimulated salivation after 3.2, increased heart rate after 6.4, and near point of vision after 12.8 mg. Six of 8 subjects reported micturition difficulties after a dose of 12.8 mg. The lack of a direct relationship between tolterodine blood serum concns. and effects on stimulated salivation suggested the presence of pharmacol. active metabolite(s).

IT **194482-44-5**
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(pharmacokinetics and pharmacodynamics of tolterodine in man)

RN 194482-44-5 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-hydroxy- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



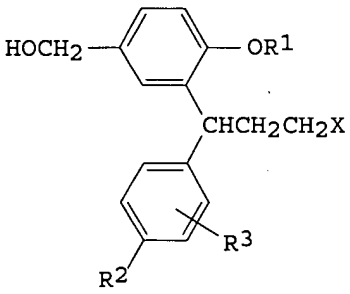
L9 ANSWER 14 OF 14 CAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1994:508197 CAPLUS
DOCUMENT NUMBER: 121:108197
TITLE: Preparation of 3,3-diphenylpropylamines and their use
INVENTOR(S): Johansson, Rolf Arne; Moses, Pinchas; Nilverbant, Lisbeth; Sparf, Bengt Aake
PATENT ASSIGNEE(S): Kabi Pharmacia AB, Swed.
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9411337	A1	19940526	WO 1993-SE927	19931105
W: AU, CA, FI, HU, JP, NO, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2148827	AA	19940526	CA 1993-2148827	19931105
AU 9454380	A1	19940608	AU 1994-54380	19931105
AU 672458	B2	19961003		
EP 667852	A1	19950823	EP 1993-924876	19931105
EP 667852	B1	19980408		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 08503208	T2	19960409	JP 1994-511977	19931105
JP 3343256	B2	20021111		
HU 72742	A2	19960528	HU 1995-1329	19931105
AT 164828	E	19980415	AT 1993-924876	19931105
ES 2117155	T3	19980801	ES 1993-924876	19931105
FI 9502179	A	19950505	FI 1995-2179	19950505
NO 9501775	A	19950505	NO 1995-1775	19950505
US 5559269	A	19960924	US 1995-432113	19950505
US 5686464	A	19971111	US 1996-684638	19960722

PRIORITY APPLN. INFO.: SE 1992-3318 A 19921106
WO 1993-SE927 W 19931105
US 1995-432113 A3 19950505

OTHER SOURCE(S): MARPAT 121:108197
GI



I

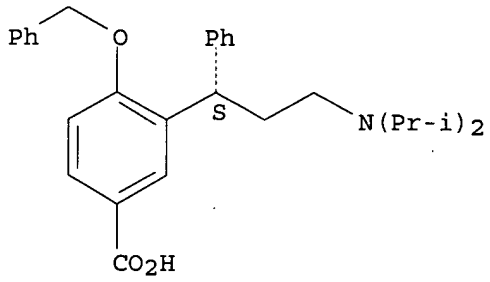
AB Title compds. I (R1 =H, Me; R2, R3 = H, Me, MeO, HO, H2NCO, H2NSO2, halo; X = R4R5N wherein R4, R5 = non-arom. hydrocarbyl and which together contain at least three carbon atoms, or R4R5N = heterocyclyl), salts, optical isomers, racemic mixt. and individual enantiomers are useful as anticholinergics. P-Br-C6H4OH, PhCH:CHCO2H, AcOH and H2SO4 were refluxed to give 6-bromo-4-phenyl-3,4-dihydrocoumarin which was converted in 4 steps to N,N-diisopropyl3-(2-benzyloxy-5-brophenyl)-3-phenylpropylamine (II). II was resolved to the (-)-isomer and converted in 4 steps to (-)-I

[R1 = PhCH2, R2 = R3 = H, X = (Me2CH)2N].(-) mandelate salt (III). In tests for anticholinergic effect, III produced a dose-dependent inhibition of the acetylcholine-induced effect on the bladder which was about 10 times more efficient than that of a prior art analog.

IT **156755-32-7P 156755-33-8P 156755-34-9P 156755-35-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(prepn. and reaction of, in prepn. of anticholinergics)

RN 156755-32-7 CAPLUS
CN Benzoic acid, 3-[(1S)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, hydrochloride (9CI) (CA INDEX NAME)

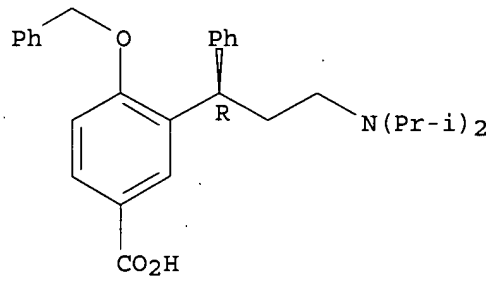
Absolute stereochemistry. Rotation (+).



○ HCl

RN 156755-33-8 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, hydrochloride (9CI) (CA INDEX NAME)

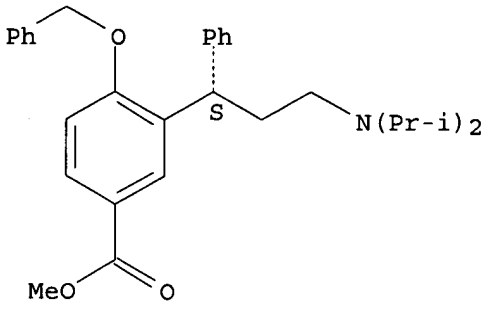
Absolute stereochemistry. Rotation (-).



◎ HCl

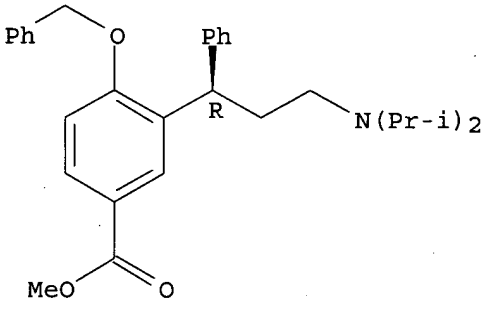
RN 156755-34-9 CAPLUS
CN Benzoic acid, 3-[(1S)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (+).



RN 156755-35-0 CAPLUS
CN Benzoic acid, 3-[(1R)-3-[bis(1-methylethyl)amino]-1-phenylpropyl]-4-(phenylmethoxy)-, methyl ester (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



=> logoff
ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF
LOGOFF? (Y)/N/HOLD:y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	72.26	522.12

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-9.11	-9.11

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PTO/SB/21 (03-03)
Approved for use through 04/30/2003. OMB 0651-0031
U.S. Patent and Trademark Office ; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/130,214
Filing Date	May 14, 2002
First Named Inventor	C. Meese
Art Unit	1614
Examiner Name	Not Yet Assigned
Total Number of Pages in This Submission	7
Attorney Docket Number	58827 (45107)

ENCLOSURES (*Check all that apply*)

- ☐ Fee Transmittal Form
- ☐ Fee Attached
- ☐ Amendment/Reply
- ☐ After Final
- ☐ Affidavits/declaration(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☐ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts/ Incomplete Application
- ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☑ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
- ☐ After Allowance Communication to a Technology Center (TC)
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to TC **(Appeal Notice, Brief, Reply Brief)**
- ☐ Proprietary Information
- ☐ Status Letter
- ☑ Other Enclosure(s) (please Identify below): Statement Under 37 CFR 3.73(b)

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual	Edwards & Angell, LLP Christine C. O'Day
Signature	Christine C. O'Day
Date	5-19-03

CERTIFICATE OF TRANSMISSION/MAILING

I hereby certify that this correspondence is being facsimile transmitted to the USPTO or deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, DC 20231 on this date: _____

Typed or printed	Susan M. Dillon		
Signature	Susan M Dillon	Date	5/19/03

If you need assistance in completing the form, call 1-800-PTO-9199 (1-800-786-9199) and select option 2.

Practitioner's Docket No. 58827

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

[X]	In re application of:	C. Meese		
	Serial No.:	10/130,214	Group No.:	1614
	Filed:	May 14, 2002	Examiner:	Not Yet Assigned
	For:	STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES		

**NOTE: Insert name(s) of all inventor(s) and title also for patent.*

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

POWER OF ATTORNEY BY ASSIGNEE OF ENTIRE INTEREST
(REVOCATION OF PRIOR POWERS)

As assignee of record of the entire interest of the above identified
[X] application,
[ ] patent,

REVOCATION OF PRIOR POWERS OF ATTORNEY

all powers of attorney previously given are hereby revoked and

NEW POWER OF ATTORNEY

the following attorney(s) and/or agent(s) are hereby appointed to prosecute and transact all business in the Patent and Trademark Office connected therewith.

(list name and registration number)

Peter F. Corless	Reg. No. 33,860	David A. Tucker	Reg. No. 27,840
Christine C. O'Day	Reg. No. 38,256	John J. Penny, Jr.	Reg. No. 36,984
David G. Conlin	Reg. No. 27,026	John B. Alexander	Reg. No. 48,399
George W. Neuner	Reg. No. 26,964	Steven M. Jensen	Reg. No. 42,693
Linda M. Buckley	Reg. No. 31,003	Kathryn A. Piffat	Reg. No. 34,901
William J. Daley, Jr.	Reg. No. 35,487	Richard J. Roos	Reg. No. 45,053
Cara Z. Lowen	Reg. No. 38,227	Dianne M. Rees	Reg. No. 45,281
Robert L. Buchanan	Reg. No. 40,927	George W. Hartnell, III	Reg. No. 42,639
Lisa Swiszcz Hazzard	Reg. No. 44,368	Howard M. Gitten	Reg. No. 32,138
J. Mark Konieczny	Reg. No. 47,715	Jennifer K. Rosenfield	Reg. No. 53,531
Gregory B. Butler	Reg. No. 34,558	Richard J. Roos	Reg. No. 45,053

(check the following item, if applicable)

[ ] Attached, as part of this power of attorney, is the authorization of the above-named attorney(s) to accept and follow instructions from my representative(s).

SEND CORRESPONDENCE TO:
Peter F. Corless
P.O. Box 9169
Boston, MA 02209
USA

DIRECT TELEPHONE CALLS TO:
Peter F. Corless
(617) 439-4444

Customer No.:

Schwarz Pharma AG .
(type or print identity of assignee of entire interest)
Alfred-Nobel-Strasse 10
Address
40789 Monheim, Germany

[X] Recorded in PTO on May 14, 2002
Reel 013122
Frame 0883
[ ] Recorded herewith

ASSIGNEE STATEMENT

Attached to this power is a "STATEMENT UNDER 37 C.F.R. 3.73(b)."

Signature

Date: 25 April 2003

K.-D. Hommerich D.W. Schacht
(type or print name of person authorized to sign on behalf of assignee)

Authorized Officer Assistant Manager
Title

NOTE: The assignee of the entire interest may revoke previous powers and be represented by an attorney of his or her selection. 37 C.F.R. 1.36.

(check the following item, if it forms a part of this power of attorney)

[ ] Added page—Authorization of attorney(s) to accept and follow instructions from representative.

Practitioner's Docket No. 58827

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

[X]	In re application of:	C. Meese		
	Serial No.:	10/130,214	Group No.:	1614
	Filed:	May 14, 2002	Examiner:	Not Yet Assigned
	For:	STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

STATEMENT UNDER 37 C.F.R. 3.73(b) ESTABLISHING RIGHT OF ASSIGNEE TO TAKE ACTION

CERTIFICATION UNDER 37 C.F.R. §§ 1.8(a) and 1.10*
*(When using Express Mail, the Express Mail label number is **mandatory**; Express Mail certification is optional.)*

I hereby certify that, on the date shown below, this correspondence is being:

MAILING

Γ deposited with the United States Postal Service in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

37 C.F.R. § 1.8(a)

Γ with sufficient postage as first class mail.

37 C.F.R. § 1.10*

Γ as AExpress Mail Post Office to Addressee≅ Mailing Label No. _____ **(mandatory)**

TRANSMISSION

Γ transmitted by facsimile to the Patent and Trademark Office.

_____
Signature

Date:_____

_____
(type or print name of person certifying)

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

patent application, ..., patent, registration, or reexamination proceeding, the assignee must establish its ownership of the property to the satisfaction of the Commissioner. Ownership is established by submitting to the Office, in the Office file related to the matter in which action is sought to be taken, documentary evidence of a chain of title from the original owner to the assignee (e.g., copy of an executed assignment submitted for recording) or by specifying (e.g., reel and frame number) where such evidence is recorded in the Office. The submission establishing ownership must be signed by a party authorized to act on behalf of the assignee. Documents submitted to establish ownership may be required to be recorded as a condition to permitting the assignee to take action in a matter pending before the Office.≅

NOTE: ASection 3.73(b) is amended to remove the sentence requiring an assignee to specifically state that the evidentiary documents have been reviewed and to certify that title is in the assignee seeking to take action. The sentence is deemed to be unnecessary in view of the amendment to ∋∋ 1.4(d) and 10.18.≅ Notice of Oct. 10, 1997, 62 Fed. Reg. 53,131, at 53,174.

1. The assignee(s) of the entire right, title and interest hereby seek(s) to take action in the PTO in this matter.

IDENTIFICATION OF ASSIGNEE

2. Schwarz Pharma AG
Name of assignee

Corporation
Type of assignee, e.g., corporation, partnership, university, government agency, etc.

PERSON AUTHORIZED TO SIGN

3. K.-D. Hommerich D.W. Schacht
(type name of person authorized to sign on behalf of assignee)
Authorized Officer Assistant Manager
Title of person authorized to sign

NOTE: The Notice of April 30, 1993 (1150 O.G. 62-64) points out:

A The statement under 37 CFR 3.73(b) may be signed on behalf of the assignee in the following two manners if the assignee is an organization (e.g., corporation, partnership, university, government agency, etc.).

A(1) The statement may be signed by a person in the organization having apparent authority to sign on behalf of the organization. An officer (president, vice-president, secretary, or treasurer) is presumed to have authority to sign on behalf of the organization. The signature of the chairman of the board of directors is acceptable, but not the signature of an individual director. A person having a title (manager, director, administrator, general counsel) that does not clearly set forth that person as an officer of the assignee is not presumed to be an officer of the assignee or to have authority to sign the statement on behalf of the assignee. A power of attorney from the inventors in an organization to a practitioner to prosecute a patent application does not make the practitioner an official of an assignee or empower the practitioner to sign the statement on behalf of the assignee.

A(2) The statement may be signed by any person, if the statement includes an averment that the person is empowered to sign the statement on behalf of the assignee and, if not signed by a registered practitioner, the statement must be in oath or declaration form. Where a statement does not include such an averment, and the person signing does not hold a position in the organization that would give rise to a presumption that the person is empowered to sign the statement on behalf of the assignee, evidence of the person=s authority to sign will be

required.≅

(complete the following, if applicable)

[X] I, the person signing below, state that I am empowered to sign this statement on behalf of the assignee.

BASIS OF ASSIGNEE'S INTEREST

Ownership by the assignee is established as follows:

A.

1. [X] An assignment from the inventor(s) of the matter identified above, which was recorded in the PTO at 05/14/02
   Reel 013122, Frame 0883

2. [ ] Other:

AND/OR

B. [ ] A chain of title from the inventor(s) to the current assignee as shown below:

1. From: _____
   Name of inventor(s)
   To: _____
   Recorded in PTO: Reel _____, Frame _____

2. From: _____
   Name of inventor(s) or assignee
   To: _____
   Recorded in PTO: Reel _____, Frame _____

3. From: _____
   Name of inventor(s) or assignee
   To: _____
   Recorded in PTO: Reel _____ Frame _____

(check item below, and add details, if applicable)

[ ] Additional documents in the chain of title are listed in the attached Supplemental Sheet.

COPIES OF DOCUMENTS IN CHAIN OF TITLE

(complete this item, if copies are being sent)

[X] Copies of the assignment(s) or other document(s) in the chain of title are attached as follows:

[X]	A	[X]	1	[ ]	2		
[ ]	B	[ ]	1	[ ]	2	[ ]	3

Signature of authorized person

K.-D. Hommerich D.W. Schacht

(type or print name of authorized person)

Authorized Officer Assistant Manager

Title of authorized person

SIGNATURE OF PRACTITIONER

Reg. No.: 38,256

Christine C. O'Day

(type or print name of practitioner)

Tel. No.: (617) 439-4444

P.O. Box 9169

P.O. Address

Customer No.: 21874

Boston, MA 02209

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/130,214	05/14/2002	Claus Meese	41946/32854

CONFIRMATION NO. 9833

Peter F. Corless
P.O Box 9169
Boston, MA 02209

OC000000010151521

#9

Date Mailed: 05/30/2003

NOTICE OF ACCEPTANCE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/22/2003.

The Power of Attorney in this application is accepted. Correspondence in this application will be mailed to the above address as provided by 37 CFR 1.33.

N. Villa

NORMA M VILLARIVERA
1641 (703) 308-0377

OFFICE COPY

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO./TITLE
10/130,214	05/14/2002	Claus Meese	41946/32854

CONFIRMATION NO. 9833

21888
THOMPSON COBURN, LLP
ONE FIRSTAR PLAZA
SUITE 3500
ST LOUIS, MO 63101

OC000000010151431

#9

Date Mailed: 05/30/2003

NOTICE REGARDING CHANGE OF POWER OF ATTORNEY

This is in response to the Power of Attorney filed 05/22/2003.

- The Power of Attorney to you in this application has been revoked by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record(37 CFR 1.33).

N. C. Villa

NORMA M VILLARIVERA
1641 (703) 308-0377

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UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents, Box PCT
United States Patent and Trademark Office
Washington, D.C. 20231
www.uspto.gov

U.S. APPLICATION NUMBER NO.	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
10/130,214	Claus Meese	41946/32854

INTERNATIONAL APPLICATION NO.	
PCT/EP00/11309	
I.A. FILING DATE	PRIORITY DATE
11/15/2000	11/16/1999

21888
THOMPSON COBURN, LLP
ONE FIRSTAR PLAZA
SUITE 3500
ST LOUIS, MO 63101

CONFIRMATION NO. 9833
371 ACCEPTANCE LETTER

OC000000008567756

Date Mailed: 08/05/2002

NOTICE OF ACCEPTANCE OF APPLICATION UNDER 35 U.S.C 371 AND 37 CFR 1.494 OR 1.495

The applicant is hereby advised that the United States Patent and Trademark Office in its capacity as an Elected Office (37 CFR 1.495) , has determined that the above identified international application has met the requirements of 35 U.S.C. 371, and is ACCEPTED for national patentability examination in the United States Patent and Trademark Office.

The United States Application Number assigned to the application is shown above and the relevant dates are:

05/14/2002	05/14/2002
DATE OF RECEIPT OF 35 U.S.C. 371(c)(1), (c)(2) and (c)(4) REQUIREMENTS	DATE OF RECEIPT OF ALL 35 U.S.C. REQUIREMENTS

A Filing Receipt (PTO-103X) will be issued for the present application in due course. **THE DATE APPEARING ON THE FILING RECEIPT AS THE " FILING DATE" IS THE DATE ON WHICH THE LAST OF THE 35 U.S.C. 371 REQUIREMENTS HAS BEEN RECEIVED IN THE OFFICE. THIS DATE IS SHOWN ABOVE.** *The filing date of the above identified application is the international filing date of the international application (Article 11(3) and 35 U.S.C. 363).* Once the Filing Receipt has been received, send all correspondence to the Group Art Unit designated thereon.

The following items have been received:

- U.S. Basic National Fee
- Assignee Statement
- Copy of IPE Report
- Copy of references cited in ISR
- Copy of the International Application
- Copy of the International Search Report
- Information Disclosure Statements
- Oath or Declaration
- Preliminary Amendments

Applicant is reminded that any communications to the United States Patent and Trademark Office must be mailed to the address given in the heading and include the U.S. application no. shown above (37 CFR 1.5)

BARBARA A CAMPBELL
Telephone: (703) 305-3631

PART 3 - OFFICE COPY

FORM PCT/DO/EO/903 (371 Acceptance Notice)

10-15-02 1614

TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT (Under 37 CFR 1.97(b) r 1.97(c))	Docket No. 41946/32854

In Re Application: Claus Meese

Serial No.	Filing Date	Examiner	Group Art Unit
10/130,214	05/14/2002	~~Not Assigned~~ TUCKER, Z. ~~1614~~	~~1614~~ 1624

Payment of Fee

(Only complete if Applicant elects to pay the fee set forth in 37 CFR 1.17(p))

☐ A check in the amount of is attached.

☒ The Assistant Commissioner is hereby authorized to charge and credit Deposit Account No. 20-0823 as described below. A duplicate copy of this sheet is enclosed.

- ☐ Charge the amount of
- ☒ Credit any overpayment.
- ☒ Charge any additional fee required.

Certificate of Transmission by Facsimile*

I certify that this document and authorization to charge deposit account is being facsimile transmitted to the United States Patent and Trademark Office (Fax No.) on

(Date)

Signature

Typed or Printed Name of Person Signing Certificate

Certificate of Mailing by Express Mail

I certify that this document and fee is being deposit d on November 13, 2002 with the U.S. Postal Service as Express mail under 37 C.F.R. 1.8 and addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231. **Express Mail No. EL948415117US**

Signature of Person Mailing Correspondence

Paul A. Lesko

Typed or Printed Name of Person Mailing Certificate

***This certificate may only be used if paying by deposit account.**

Signature

Dated: November 13, 2002

Paul A. Lesko, Reg. #45364
Thompson Coburn LLP
One US Bank Plaza
St. Louis, Missouri 63101
314-552-6443
314-552-7443 FAX

cc: Customer No. 021888

P10C/REV02

TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT (Under 37 CFR 1.97(b) or 1.97(c))	Docket No. 41946/32854

In Re Application Of:
Claus Meese

Serial No.	Filing Date	Examiner	Group Art Unit
10/130,214	05/14/2002	~~Not Assigned~~ TUCKER, Z.	~~1614~~ 1624

Title:
Stable Salts of Novel Derivatives of 3,3-Diphenylpropylamines

Address to:
Assistant Commissioner for Patents
Washington, D.C. 20231

37 CFR 1.97(b)

1. ☒ The Information Disclosure Statement submitted herewith is being filed within three months of the filing of a national application other than a continued prosecution application under 37 CFR 1.53(d); within three months of the date of entry of the national stage as set forth in 37 CFR 1.491 in an international application; before the mailing of a first Office Action on the merits, or before the mailing of a first Office Action after the filing of a request for continued examination under 37 CFR 1.114.

37 CFR 1.97(c)

2. ☐ The Information Disclosure Statement submitted herewith is being filed after the period specified in 37 CFR 1.97(b), provided that the Information Disclosure Statement is filed before the mailing date of a Final Action under 37 CFR 1.113, a Notice of Allowance under 37 CFR 1.311, or an Action that otherwise closes prosecution in the application, and is accompanied by one of:

   ☐ the statement specified in 37 CFR 1.97(e);

   OR

   ☐ the fee set forth in 37 CFR 1.17(p).

P10A/REV02

Please type a plus sign (+) inside this box → ⊞

PTO/SB/21 (08-00)
Approved for use through 10/31/2002. OMB 0651-0031
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Numb r	10/130,214
Filing Date	May 14, 2002
First Named Inventor	Meese
Group Art Unit	1614
Examiner Name	Not Assigned
Total Number of Pages in This Submission: 1	Attorney Docket No. 41946/32854

ENCLOSURES *(check all that apply)*

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Signature	
Dat	November 13, 2002

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(57) Abstract

The invention concerns novel derivatives of 3,3–diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs. More particularly, the invention relates to novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to existing drugs such as oxybutynin and tolterodine, methods for their preparation, pharmaceutical compositions containing them, a method of using said compouds and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

NOT PRIOR ART.

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Description

Novel derivatives of 3,3-diphenylpropylamines

The present invention relates to novel derivatives of 3,3-diphenylpropylamines, methods for their preparation, pharmaceutical compositions containing the novel compounds, and the use of the compounds for preparing drugs.

In man, normal urinary bladder contractions are mediated mainly through cholinergic muscarinic receptor stimulation. There is reason to believe that muscarinic receptors mediate not only normal bladder contractions, but also the main part of the contractions in the overactive bladder resulting in symptoms such as urinary frequency, urgency and urge incontinence. For this reason, antimuscarinic drugs have been proposed for the treatment of bladder overactivity.

Among the antimuscarinic drugs available on the market, oxybutynin is currently regarded as the gold standard for pharmacological treatment of urge incontinence and other symptoms related to bladder overactivity. The effectiveness of oxybutynin has been demonstrated in several clinical studies, but the clinical usefulness of oxybutynin is limited due to antimuscarinic side effects. Dryness of the mouth is the most common experienced side effect which may be severe enough to

result in poor compliance or discontinuation of treatment (Andersson, K.-E., 1988, Current concepts in the treatment of disorders of micturition, Drugs 35, 477-494; Kelleher et al. 1994).

Tolterodine is a new, potent and competitive, muscarinic receptor antagonist intended for the treatment of urinary urge incontinence and detrusor hyperactivity. Preclinical pharmacological data show that tolterodine exhibits a favourable tissue selectivity in vivo for the urinary bladder over the effect on the salivation (Nilvebrant et al., 1997, Tolterodine - a new bladder-selective antimuscarinic agent, Eur. J. Pharmacol. 327 (1997), 195-207), whereas oxybutynin exhibits the reversed selectivity. Tolterodine is equipotent to oxybutynin at urinary bladder muscarinic receptors and the favourable tissue selectivity of tolterodine demonstrated in the preclinical studies has been confirmed in clinical studies. Thus a good clinical efficacy has been combined with a very low number of incidences of dry mouth and antimuscarinic side effects.

A major metabolite of tolterodine, the 5-hydroxymethyl derivative is also a potent muscarinic receptor antagonist and the pharmacological in vitro and in vivo profiles of this metabolite are almost identical to those of tolterodine (Nilvebrant et al., 1997, Eur. J. Pharmacol. 327 (1997), 195-207). Combined pharmacological and pharmacokinetic data indicate that it is most likely that the metabolite gives a major contribution to the clinical effect in most patients.

WO 94/11337 proposes the active metabolite of tolterodine as a new drug for urge incontinence. Administration of the active metabolite directly to patients has the advantage com-

pared to tolterodine that only one active principle (compound) has to be handled by the patient which normally should result in a lower variation in efficacy and side effects between patients and lower risk of interaction with other drugs.

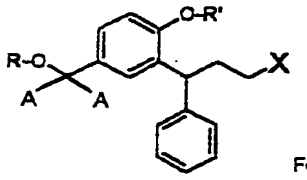
However, the introduction of an additional hydroxy group in the tolterodine results in an increased hydrophilic property of the new compounds (3,3-diphenylpropylamines) compared to the parent compounds which normally results in a lower absorption/bioavailability, leading to pre-systemic side effects or interactions due to non-absorbed antimuscarinic drug. In a method to circumvent this disadvantage, different prodrugs of the metabolite have been synthesized and tested for their antimuscarinic activity, potential absorption through biological membranes and enzymatic cleavage.

It is an object of the present invention to provide novel derivatives of 3,3-diphenylpropylamines. It is a further object of the present invention to provide new derivatives of 3,3-diphenylpropylamines which will be more useful as prodrugs for treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms while avoiding the disadvantage of a too low absorption through biological membranes of the drugs or an unfavourable metabolism.

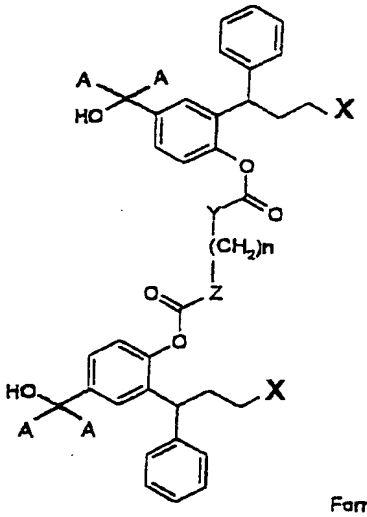
A further object of the invention is to provide novel prodrugs of antimuscarinic agents with superior pharmacokinetic properties compared to present drugs as oxybutynin and tolterodine, methods for preparing thereof, pharmaceutical compositions containing them, a method of using said compounds

and compositions for the treatment of urinary incontinence, gastrointestinal hyperactivity (irritable bowel syndrome) and other smooth muscle contractile conditions.

According to the present invention, novel 3,3-diphenylpropylamines are provided, which are represented by the general formulae I and VII'



Formula I



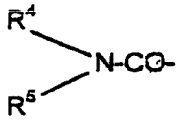
Formula VII'

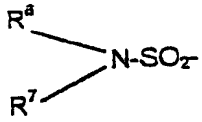
wherein R and R' are independently selected from

a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d)  wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

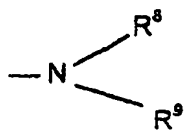
e)  wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unstubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl, preferably phenyl,

with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen,

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12

and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

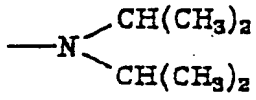
The aforementioned compounds can form salts with physiologically acceptable organic and inorganic acids. Furthermore, the aforementioned compounds comprise the free bases as well as the salts thereof. Examples of such acid addition salts include the hydrochloride, hydrobromide and the like.

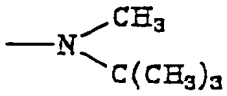
When the novel compounds are in the form of optical isomers, the invention comprises the racemic mixture as well as the individual isomers as such.

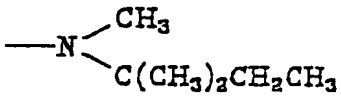
Preferably each of R^8 and R^9 independently signifies a saturated hydrocarbyl group, especially saturated aliphatic hydrocarbyl groups such as C_{1-8}-alkyl, especially C_{1-5}-alkyl, or adamantyl, R^8 and R^9 together comprising at least three, preferably at least four carbon atoms.

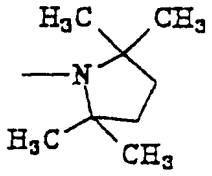
According to another embodiment of the invention, at least one of R^8 and R^9 comprises a branched carbon chain.

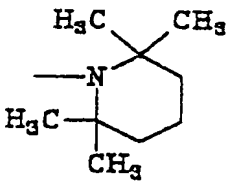
Presently preferred tertiary amino groups X in formula I include the following groups a) to h):

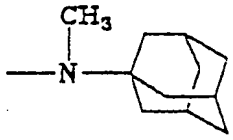
a) 

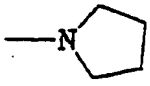
b) 

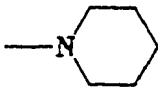
c) 

d) 

e) 

f) 

g) 

h) 

Group a) is particularly preferred.

The aforementioned tertiary amino groups X are described in WO 94/11337 and the compounds according to the present invention can be obtained by using the corresponding starting compounds.

In the compounds according to the present invention, the term "alkyl" preferably represents a straight-chain or branched-chain hydrocarbon group having 1 to 6 carbon atoms. Such hydrocarbon groups may be selected from methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl. The term "cycloalkyl" denotes a cyclic hydrocarbon group having 3 to 10 carbon atoms which may be substituted conveniently.

The term "substituted or unsubstituted benzyl" denotes a benzyl group $-CH_2-C_6H_5$ which is optionally substituted by one or more substituents on the phenyl ring. Suitable substituents are selected from alkyl, alkoxy, halogen, nitro and the like. Suitable halogen atoms are fluorine, chlorine and iodine atoms. Preferred substituted benzyl groups are 4-methylbenzyl, 2-methylbenzyl, 4-methoxybenzyl, 2-methoxybenzyl, 4-nitrobenzyl, 2-nitrobenzyl, 4-chlorobenzyl and 2-chlorobenzyl.

In the compounds according to the present invention the term "C_1-C_6 alkylcarbonyl" denotes a group R-C(=O)- wherein R is an alkyl group as defined hereinbefore. Preferred C_1-C_6 alkylcarbonyl groups are selected from acetyl, propionyl, isobutyryl, butyryl, valeroyl and pivaloyl. The term "cycloalkylcarbonyl" denotes a group R-C(=O)- wherein R is a cyclic hydrocarbon group as defined hereinbefore. The same counts to the selected carbonyl groups.

The term "aryl" denotes an aromatic hydrocarbon group such as phenyl- (C_6H_5-), naphthyl- ($C_{10}H_7$-), anthryl- ($C_{14}H_9$-), etc. Preferred aryl groups according to the present invention are phenyl and naphthyl with phenyl being particularly preferred.

The term "benzoyl" denotes an acyl group of the formula -CO-C_6H_5 wherein the phenyl ring may have one or more substituents.

Preferred substituents of the aryl group and in particular of the phenyl group are selected from alkyl, alkoxy, halogen and *nitro*. As substituted benzoyl groups 4-methylbenzoyl, 2-methylbenzoyl, 4-methoxybenzoyl, 2-methoxybenzoyl, 4-chlorobenzoyl, 2-chlorobenzoyl, 4-nitrobenzoyl and 2-nitrobenzoyl may be mentioned.

The term "C_1-C_6 alkoxycarbonyl" refers to a group ROC(=O)- wherein R is an alkyl group as defined hereinbefore. Preferred C_1-C_6 alkoxycarbonyl groups are selected from $CH_3OC(=O)$-, C_2H_5-OC(=O)-, $C_3H_7OC(=O)$- and $(CH_3)_3COC(=O)$- and alicyclic alkyloxycarbonyl.

The term "amino acid residue" denotes the residue of a naturally occurring or synthetic amino acid. Particularly preferred amino acid residues are selected from the group consisting of glycyl, valyl, leucyl, isoleucyl, phenylalanyl, prolyl, seryl, threonyl, methionyl, hydroxyprolyl.

The amino acid residue may be substituted by a suitable group and as substituted amino acid residues, benzoylglycyl and N-acetylglycyl may be mentioned.

The term "carbohydrate" denotes the residue of a polyhydroxy aldehyde or polyhydroxy ketone of the formula $C_nH_{2n}O_n$ or $C_n(H_2O)_n$ and correponding carbohydrate groups are, for example, described in Aspinal, The Polysaccharides, New York: Academic Press 1982, 1983. A preferred carbohydrate group in the compounds according to the present invention is a glucuronosyl group, in particular a 1β-D-glucuronosyl group.

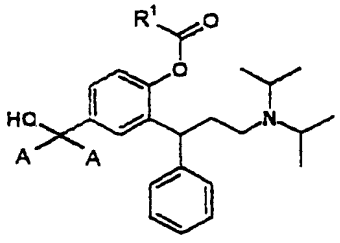
The term "LG" as used herein denotes a leaving group selected from halogenides, carboxylates, imidazolides and the like.

The term "Bn" as used herein denotes a benzyl group.

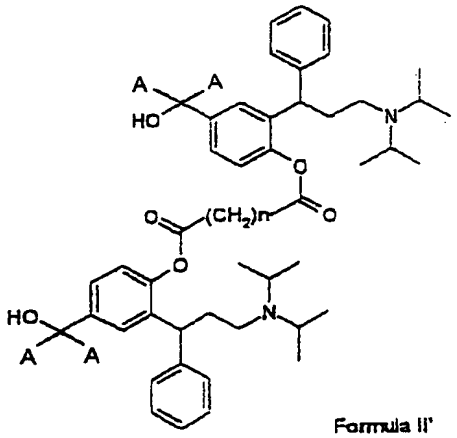
Suitable ester moieties of inorganic acids may be derived from inorganic acids such as sulfuric acid and phosphoric acid.

Preferred compounds according to the present invention are:

A) Phenolic monoesters represented by the general formulae II and II'



Formula II



Formula II'

wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

Particularly preferred phenolic monoesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

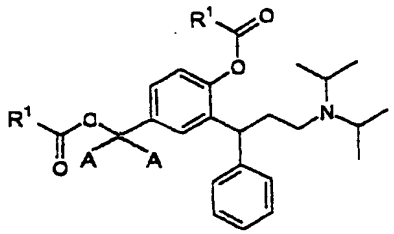
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester.

B) Identical diesters represented by the general formula III



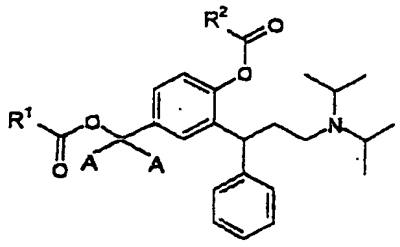
Formula III

wherein R^1 is as defined above.

Particularly preferred identical diesters are listed below:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diiso-propylamino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,
cyclic oct-4-ene-1,8-dioate of Intermediate B,
cyclic octane-1,8-dioate of Intermediate B,
poly-co-DL-lactides of Intermediate B.

C) Mixed diesters represented by the general formula IV



Formula IV

wherein R^1 is as defined above

and

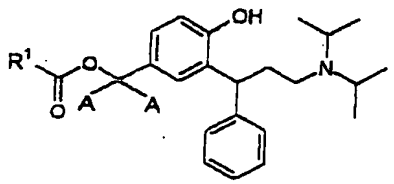
R^2 represents hydrogen, C_1-C_6 alkyl or phenyl

with the proviso that R^1 and R^2 are not identical.

Particularly preferred mixed diesters are listed below:

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

D) Benzylic monoesters represented by the general formula V



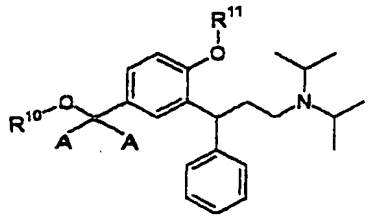
Formula V

wherein R^1 is as defined above.

Particularly preferred benzylic monoesters are listed below:

(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-propionic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxybenzyl ester,
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxybenzyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

E) Ethers and silyl ethers represented by the general formula VI



Formula VI

wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl or $-SiR_aR_bR_c$ as defined above and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

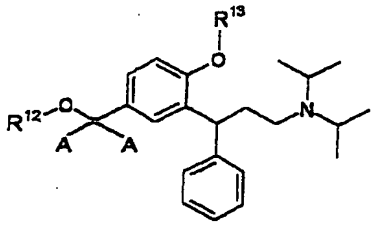
Particularly preferred ethers and silyl ethers are listed below:

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxymethylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethylphenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol,

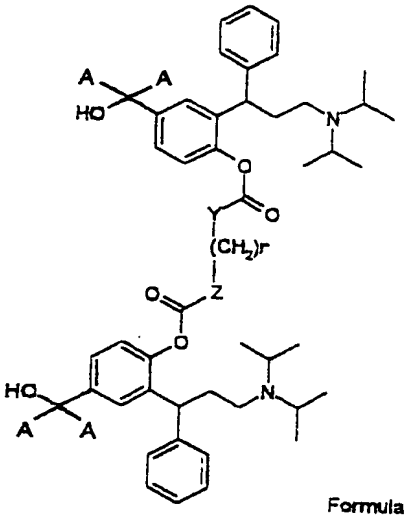
(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]-amine,
(±)-[3-(3-diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,
(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-diphenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropylamine,
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,

(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol.

F) Carbonates and carbamates represented by the general formulae VII and VIII

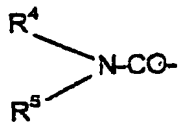


Formula VII



Formula VIII

wherein Y, Z and n are as defined above and wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



wherein R^4 and R^5 are as defined above.

Particularly preferred carbonates and carbamates are listed below:

(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,

(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-methyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,

(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N-ethylcarbamoyloxybenzyl ester,

(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,

(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,

(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,

(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,

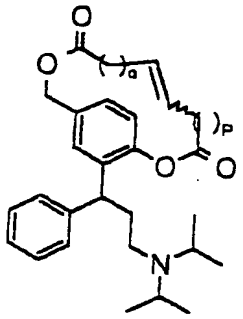
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,

(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,

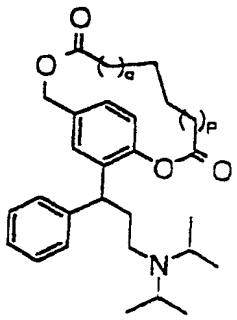
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

G) 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'



Formula IX



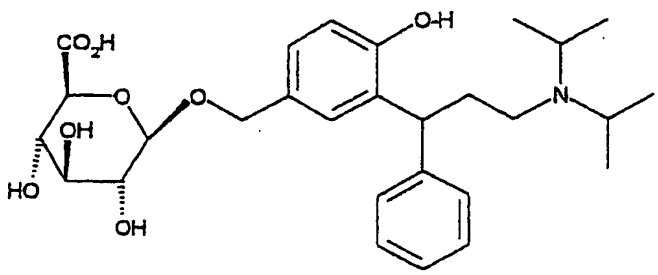
Formula IX'

wherein o and p are the same or different and represent the number of methylene units $-CH_2-$ and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol

(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula

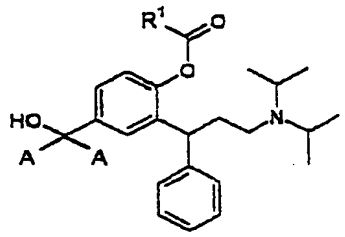


and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

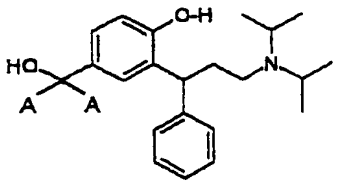
The present invention, moreover, relates to processes for the preparation of the aforementioned compounds. In particular, according to the present invention, the following processes are provided:

A process for the production of phenolic monoesters represented by the general formula II

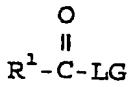


Formula II

as defined above, which comprises treatment of a compound of the formula

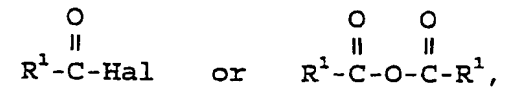


with an equivalent of an acylating agent selected from



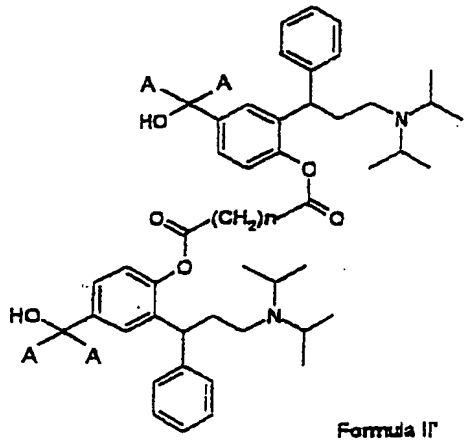
wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined above, in an inert solvent in the presence of a condensating agent.

Preferably, the acylating agent is selected from



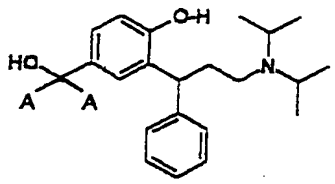
wherein Hal represents a halogen atom, preferably a chlorine atom, and R^1 is as defined above.

A process for the production of phenolic monoesters represented by the general formula II'

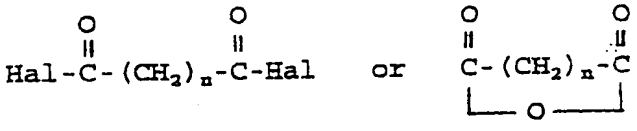


Formula II'

as defined above, which comprises treatment of two equivalents of a compound of the formula

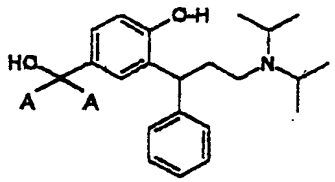


with an acylating agent selected from



wherein Hal represents a halogen atom, preferably a chlorine atom.

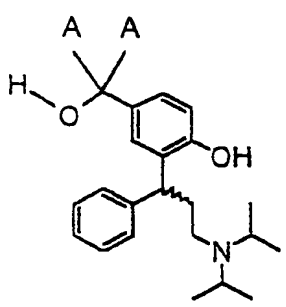
Hence, in these processes, an Intermediate B having the formula



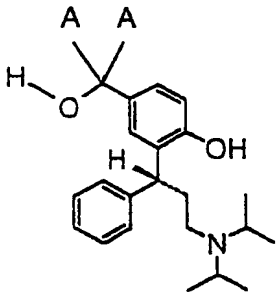
is treated with an equivalent of an acylating agent (e.g. an acyl halogenite or acyl anhydride) in an inert solvent and in the presence of a condensating agent (e.g. amine) to provide phenolic monoesters of formula II or formula II' (wherein n

is 0-12), respectively, if polyfunctional acylating agents (e.g. acid halides, preferably acid chlorides of dicarboxylic acids) are used.

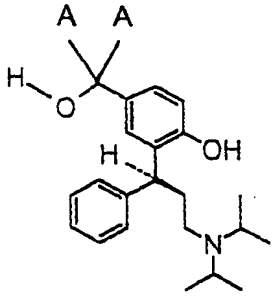
The Intermediate B as used in the processes for the production of the 3,3-diphenylpropylamines according to the present invention can be in the form of a racemic mixture or of optically active compounds in accordance with the formulae shown below:



Intermediate RS



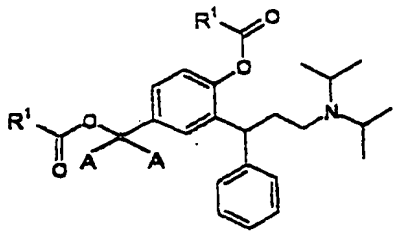
Intermediate R-(+)



Intermediate S-(-)

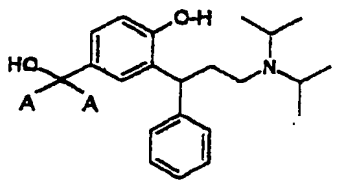
Alternatively, structures of formula II or II' may be obtained by regioselective deprotection of a protected benzylic hydroxy group (chemically or enzymatically: T. W. Greene, P. G. M. Wuts, *"Protective Groups in Organic Chemistry"*, 2nd Ed., J. Wily & Sons, New York 1991).

The identical diesters represented by the general formula III



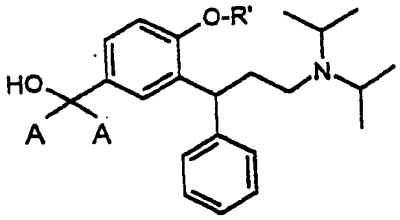
Formula III

as defined above can be prepared by a process which comprises treatment of a compound of the formula



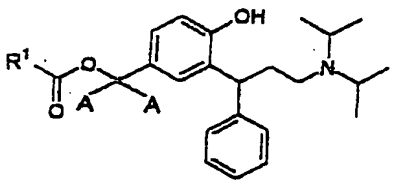
with at least two equivalents of the acylating agent R^1-C(=O)-LG as defined above.

Thus, the aforementioned di-acyl compounds are readily accessible if an at at least two-molar excess of an acylating agent is used in the above-mentioned conversion of Intermediate B or, more general, on treatment of compounds of formula I with acylating agents in the presence of suitable catalysts. In the above process, the following Intermediate A



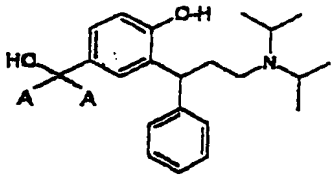
wherein R' denotes a benzyl group can be used instead of Intermediate B. The Intermediate A can be used in the form of a racemic mixture or of optically active compounds (similar to Intermediate B).

Benzylic monoestes represented by the general formula V



Formula V

wherein R^1 is as defined above can be prepared by a process which comprises treatment of a compound of the formula

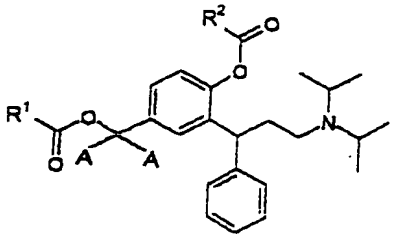


at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

Hence, this process relates to the preparation of phenols with *para* acyloxymethyl substituents (cf. formula V). These compounds can be prepared in several chemical steps from intermediates such as formula I, where R represents hydrogen and R' is hydrogen or any suitable protective group which can be removed by known methods (T. W. Greene, P.G.M. Wuts, "*Protective Groups in Organic Chemistry*", 2nd Ed., J. Wily & Sons, New York 1991) in the presence of the newly introduced substituent R^1CO. It was found, however, that the benzylic substituent R^1CO can be introduced more conveniently and in only one step if Intermediate B is treated at room tempera-

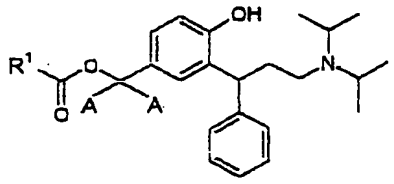
ture and under anhydrous conditions with activated esters (e.g. vinyl acylates, isopropenyl acylates) in the presence of enzymes such as lipases or esterases.

The mixed diesters represented by the general formula IV



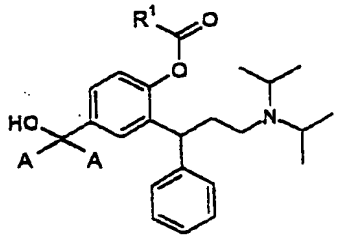
Formula IV

wherein R^1 and R^2 are as defined above can be prepared by a process which comprises acylation of the above-mentioned benzylic monoester represented by the general formula V



Formula V

wherein R^1 is as defined above or of a phenolic monoester represented by the general formula II

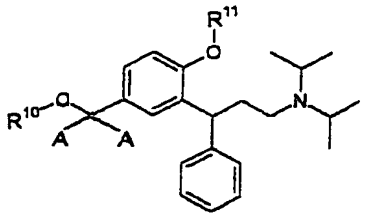


Formula II

as defined hereinbefore.

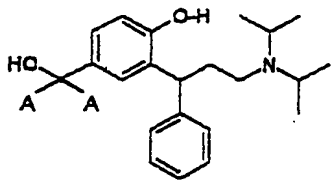
In general, mixed diesters of formula IV can be obtained by acylation of compounds of the general formula I wherein R and R' are different substituents selected from the group consisting of hydrogen, acyl residues or protecting groups that are cleavable under the acylation reaction conditions.

Ethers represented by the general formula VI



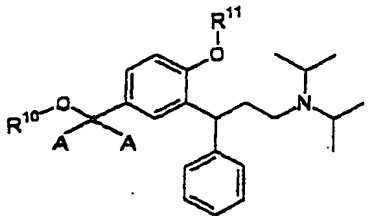
Formula VI

as defined hereinbefore wherein R^{11} is hydrogen can be prepared by a process which comprises reacting a compound of the formula



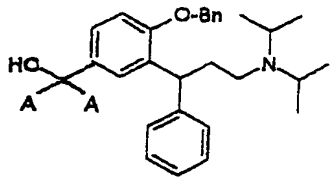
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

A further process for the preparation of ethers represented by the general formula VI

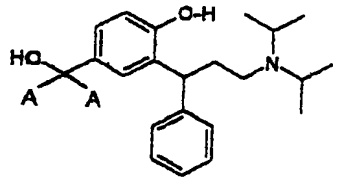


Formula VI

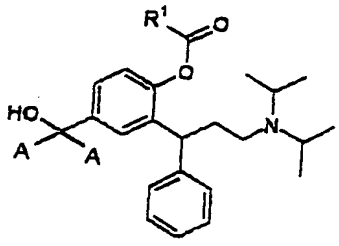
wherein R^{10} and R^{11} are as defined hereinbefore, comprises acid or base treatment of free benzylic alcohols selected from



and

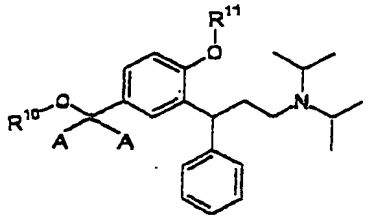


and



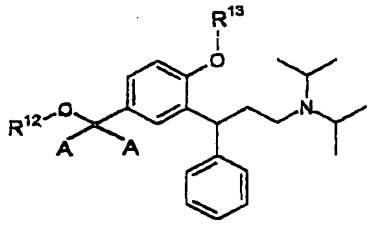
Formula II

or



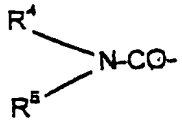
Formula VI

wherein R^{10} is hydrogen and R^{11} is as defined above or



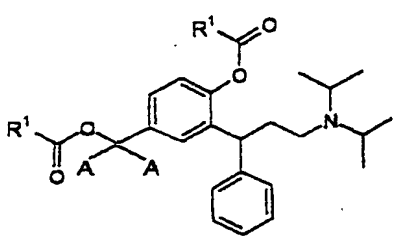
Formula VII

wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or

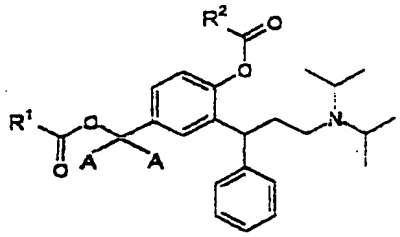


wherein R^4 and R^5 are as defined above

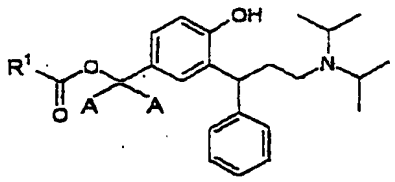
or of benzylic acylates selected from



Formula III



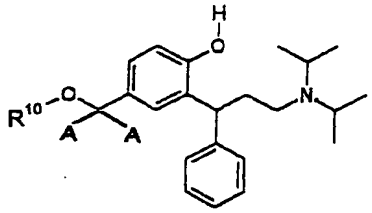
Formula IV



Formula V

wherein R^1 and R^2 are as defined hereinbefore in the presence of suitable hydroxy reagents.

Finally, ethers of formula VI can be prepared by a process which comprises treating a compound of the formula

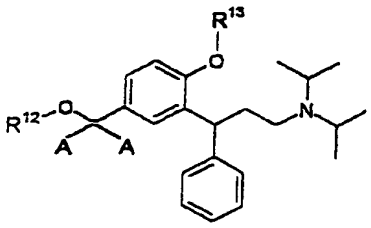


wherein R^{10} is as defined above with an alkylating agent selected from alkyl halogenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

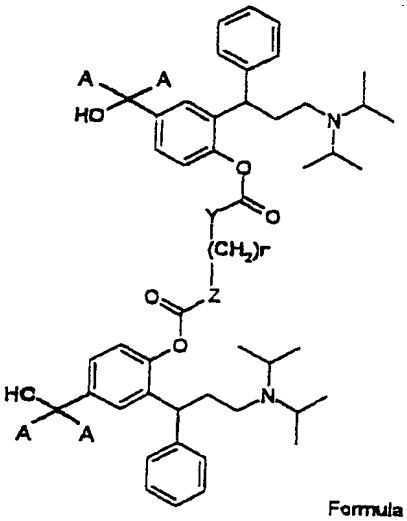
In summary, regioselective modification of the *benzylic hydroxy groups* is achieved either by acid or base treatment of benzylic acylates in the presence of suitable hydroxy reagents (e.g. alcohols) or by catalytic ether formation as described in the literature for other benzylic substrates (J.M. Saa, A. Llobera, A. Garcia-Raso, A. Costa, P.M. Deya; J. Org. Chem. **53**: 4263-4273 [1988]). Both free benzylic alcohols such as Intermediates A and B or compounds of formulas II or VI (in which R^{10} is hydrogen) or formula VII (in which R^{12} is hydrogen) as well as benzylic acylates such as formulae III, IV, V may serve as starting materials for the preparation of benzylic ethers (B. Loubinoux, J. Miazimbakana, P. Gerardin; Tetrahedron Lett. **30**: 1939-1942 [1989]).

Likewise the *phenolic hydroxy groups* are readily transformed into phenyl ethers (R^{11} = alkyl) using alkylating agents such as e.g. alkyl halogenides, alkyl sulphates, alkyl triflates or employing Mitsunobu type reaction conditions (Synthesis **1981**, 1-28). Similarly, both phenolic and alcoholic monosilyl ethers are obtained by regioselective silylation or by desilylation of bis-silyl ethers of Intermediate B as described for other compounds in the literature (J. Paladino, C. Guyard, C. Thurieau, J.-L. Fauchere, Helv. Chim. Acta **76**: 2465-2472 [1993]; Y. Kawazoe, M. Nomura, Y. Kondo, K. Kohda, Tetrahedron Lett. **26**: 4307-4310 [1987]).

Carbonates and carbamates represented by the general formulae VII and VIII

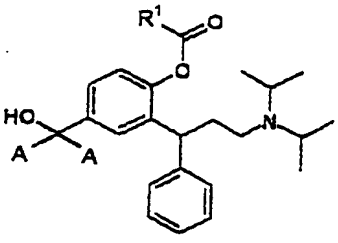


Formula VII

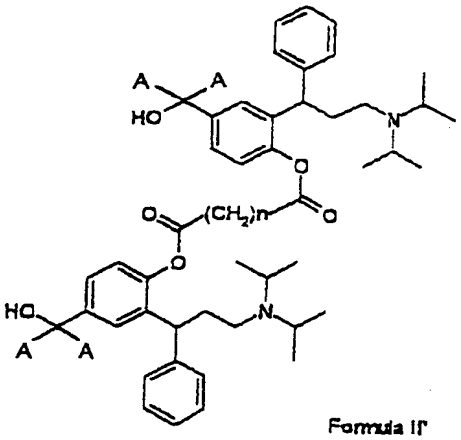


Formula VIII

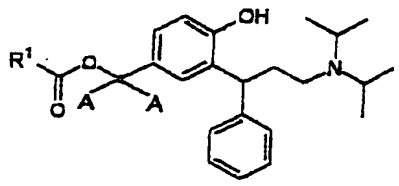
as defined hereinbefore can be prepared by a process which comprises reacting a compound selected from the group consisting of



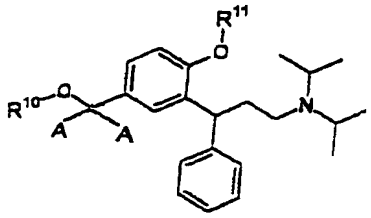
Formula II



Formula II'



Formula V



Formula VI

wherein R^1 is defined as above, n is 0 to 12, Bn is benzyl, R^{10} or R^{11} is hydrogen with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

The coupling reactions can be carried out in inert solvents over periods of several hours at temperatures from -10°C to the refluxing temperature of the solvent or reagent used to provide compounds of the general formula VII where R^{12} represents hydrogen, alkyl, aliphatic or aromatic acyl, or carbamoyl, and R^{13} represents $-C(=O)-Y-R^3$, wherein Y and R^3 represent O, S, NH and alkyl or aryl, respectively. Polyfunctional reagents give the corresponding derivatives. For example, diisocyanates or di-carbonylchlorides provide compounds of formula VIII where X, Y have the meaning of O, S, or NH and n is zero to twelve.

The invention, moreover, relates to pharmaceutical compositions comprising one or more of the aforementioned 3,3-diphenylpropylamines. In other words, the compounds according to the present invention can be used as pharmaceutically active substances, especially as antimuscarinic agents.

They can be used for preparing pharmaceutical formulations containing at least one of said compounds.

The compounds according to the present invention in the form of free bases or salts with physiologically acceptable acids, can be brought into suitable galenic forms, such as compositions for oral use, for injection, for nasal spray administration or the like, in accordance with accepted pharmaceutical procedures. Such pharmaceutical compositions according to the invention comprise an effective amount of the compounds of claims 1 to 15 in association with compatible pharmaceutically acceptable carrier materials, or diluents, as is well known in the art. The carriers may be any inert material, organic or inorganic, suitable for enteral, percutaneous or parenteral administration, such as water, gelatine, gum arabicum, lactose, microcrystalline cellulose starch, sodium starch glycolate, calcium hydrogen phosphate, magnesium stearate, talcum, colloidal silicon dioxide, and the like. Such compositions may also contain other pharmaceutically active agents, and conventional additives, such as stabilizers, wetting agents, emulsifiers, flavouring agents, buffers, and the like.

The composition according to the invention can e.g. be made up in solid or liquid form for oral administration, such as tablets, capsules, powders, syrups, elixirs and the like, in

the form of sterile solutions, suspensions or emulsions for parenteral administration, and the like.

The compounds according to the invention may be used in a patch formulation. The compounds can be administered transdermally with a reduced incidence of side effects and improved individual compliance.

The compounds and compositions can, as mentioned above, be used for the treatment of urinary incontinence and other spasmogenic conditions that are caused by muscarinic mechanisms. The dosage of the specific compound will vary depending on its potency, the mode of administration, the age and weight of the patient and the severity of the condition to be treated. The daily dosage may, for example, range from about 0.01 mg to about 5 mg, adminstered singly or multiply in doses e.g. from about 0.05 mg to about 50 g each.

The invention will be further illustrated by the following non-limiting examples and pharmacological tests.

I. Experimental

1. General

All compounds were fully characterized by ^{1}H and ^{13}C NMR spectroscopy (Bruker DPX 200). The chemical shifts reported for ^{13}C NMR spectra (50 MHz, ppm values given) refer to the solvents $CDCl_3$ (77.10 ppm), dideuterio dichloromethane (CD_2Cl_2, 53.8 ppm), CD_3OD (49.00 ppm) or hexadeuterio dimethylsulphoxide (DMSO-d_6, 39.70 ppm), respectively. ^{1}H NMR data (200 MHz, ppm) refer to internal tetramethylsilane).

Thin-layer chromatography (tlc, R_f values reported) was conducted on precoated 5x10 cm E. Merck silica gel plates (60F254), spots were visualized by fluorescence quenching or spaying with alkaline potassium permanganate solution.
Solvent systems: (1), ethyl acetate/n-hexane (30/70, v/v-%);(2), toluene/acetone/methanol/acetic acid (70/5/20/5, v/v-%); (3), n-hexane/acetone/diethylamine (70/20/10, v/v-%); (4), n-hexane/acetone/triethylamine (70/20/10, v/v-%); (5), ethyl acetate/n-hexane/2-propanol/triethylamine (60/40/20/1, v/v-%); (6), ethyl acetate/triethylamine (90/10, v/v-%); (7), cyclohexane/acetone/acetic acid (80/20/0.5, v/v-%).
Optical rotations were measured at 589.3 nm and room temperature on a Perkin Elmer Polarimeter Type 241.
Melting points (mp) reported are uncorrected and were determined on a Mettler FP 1 instrument.
IR spectra were taken from a Perkin-Elmer FTIR spectrometer Series 1610, resolution 4 cm^{-1}.
Gas chromatography-mass spectrometry (GC-MS): spectra (m/z values and relative abundance (%) reported) were recorded on a Finnigan TSQ 700 triple mass spectrometer in the positive (P-CI) or negative (N-CI) chemical ionization mode using methane or ammonia as reactant gas. Hydroxylic compounds were analyzed as their trimethylsilyl ether derivatives.
Combined liquid chromatography-mass spectrometry (LC-MS): Waters Integrety System, Thermabeam Mass Detector (EI, 70 eV), m/z values and relative abundance reported.

2. Synthesis of Intermediates A and B

3-Phenylacrylic acid 4-bromophenyl ester

An ice-cooled solution of 4-bromophenol (69.2 g) and cinnamoyl chloride (66.8 g) in dichloromethane (150 ml) was treated with triethylamine (40.6 g). After stirring for 18 hrs at

room temperature the mixture was washed with water (250 ml), 1 M aqueous HCl, and dried over anhydrous sodium sulphate. Evaporation in vacuum left solid *3-phenylacrylic acid 4-bromophenyl ester* (121.0 g, 99.8% yield), m.p. 113.3°C, tlc: (1) 0.83. NMR($CDCl_3$): 116.85, 118.87, 123.49, 128.38, 129.06, 130.90, 132.49, 134.02, 147.07, 149.84, 165.06.

(±)-6-Bromo-4-phenylchroman-2-one

A portion of the ester (60.0 g) was dissolved in a mixture of acetic acid (60 ml) and concentrated sulphuric acid (18 ml) and refluxed for 2 hrs. After cooling, the reaction mixture was poured into ice water and the product was isolated by extraction with ethylacetate. Evaporation of the solvent and recrystallization of the residue from boiling ethanol (150 ml) yielded 26.3 g (43.8% yield) of pure, crystalline *(±)-6-bromo-4-phenylchroman-2-one*, m.p. 117.8°C, tlc: (1) 0.67. NMR ($CDCl_3$): 36.56, 40.51, 117.29, 118.87, 127.47, 127.89, 128.33, 129.32, 131.07, 131.79, 139.42, 150.76, 166.84.

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester

A suspension consisting of (±)-6-bromo-4-phenylchroman-2-one (85.0 g), anhydrous potassium carbonate (46.7 g), sodium iodide (20.5 g) and benzyl chloride (40.6 g) in methanol (350 ml) and acetone (350 ml) was refluxed for 3 hrs. After evaporation of the solvents the residue was extracted with diethyl ether (2 x 300 ml) and the extract was washed with water (2 x 200 ml) and aqueous sodium carbonate. Drying (Na_2SO_4) and rotoevaporation left 121.8 g (102.1% crude yield) of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* as a light yellow oil, tlc: (1) 0.77; NMR ($CDCl_3$): 39.22, 40.53, 51.63, 70.16, 113.10, 113.77, 126.46,

126.92, 127.88, 128.08, 128.34, 128.45, 130.31, 130.55, 134.41, 136.44, 142.37, 154.94, 172.08.

(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
A solution of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenyl-propionic acid methyl ester* (0,391 g, 0,92 mmol) in ethanol (5 ml) was treated at 50°C with excess aqueous sodium hydroxide solution until the milky emulsion became clear. The reaction mixture was then acidified (pH 3), evaporated and extracted with dichloromethane. The organic extract was evaporated and the remaining oil was redissolved in a minimum of boiling ethanol. The precipitation formed after 18 hrs at 4°C was filtered off and dried in vacuo to yield 0,27 g (71.4%) of *(±)-3-(2-Benzyloxy)-5-bromophenyl)-3-phenylpropionic acid*, colourless crystals, m.p. 124.9°C; tlc: (1) 0.15 (starting material methyl ester 0.75); NMR ($CDCl_3$): 39.15, 40.26, 70.25, 113.21, 113.90, 126.62, 127.27, 127.98, 128.17, 128.47, 128.54, 130.46, 130.68, 134.34, 136.45, 142.16, 154.95, 177.65. LC-MS: 412/410 (14/11%, $M^{+\cdot}$), 394/392 (15/13%), 321/319 (17/22%), 304/302 (17/21%), 259 (24%), 194 (22%), 178 (21%), 167 (65%), 152 (49%), 92 (100%). IR (KBr): 3434, 3030, 1708, 1485, 1452, 1403, 1289, 1243, 1126, 1018, 804, 735, 698, 649. Calculated for $C_{22}H_{19}BrO_3$ (mol-wgt. 411.30): C 64.25%, H 4.66%, Br 19.43%, O 11.67%; found: C 63.72%, H 4.70%, Br 19.75%, O 11.80%.

Alternatively, the crude reaction mixture from the above described synthesis of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid methyl ester* was evaporated, redissolved in warm ethanol, and treated with excess aqueous potassium hydroxide solution. Acidification to pH 3 (conc. hydrochloric acid) and cooling to 4°C resulted in the formation of a solid, which was filtered off after 18 hrs, washed repeatedly

with water and dried to yield *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* in 82% yield.

a) Resolution of 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid

R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
Warm solutions of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* (815.6 g, 1.85 mol) and 1S,2R-(+)-ephedrine hemihydrate (232.1 g, 1.85 mol) in 2000 ml and 700 ml, respectively, of absolute ethanol were combined and then allowed to cool to 0°C. The precipitate formed was collected, washed with cold ethanol and dried in vacuum to give 553.2 g of the ephedrinium salt of the title compound (m.p. 153°C, e.e. 65% as determined by NMR and HPLC). The salt was recrystallized twice from boiling ethanol to give *R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1S,2R-(+)-ephedrinium salt* in 75% yield, colourless crystalls, m.p. 158.6°C, e.e. 97.6% (HPLC). NMR ($CDCl_3$): 9.53, 30.90, 41.54, 42.83, 61.45, 70.15, 70.42, 113.05, 113.68, 125.89, 126.03, 127.33, 127.85, 128.19, 128.28, 128.45, 129.86, 130.70, 135.91, 136.65, 140.40, 144.09, 155.20, 178.94.

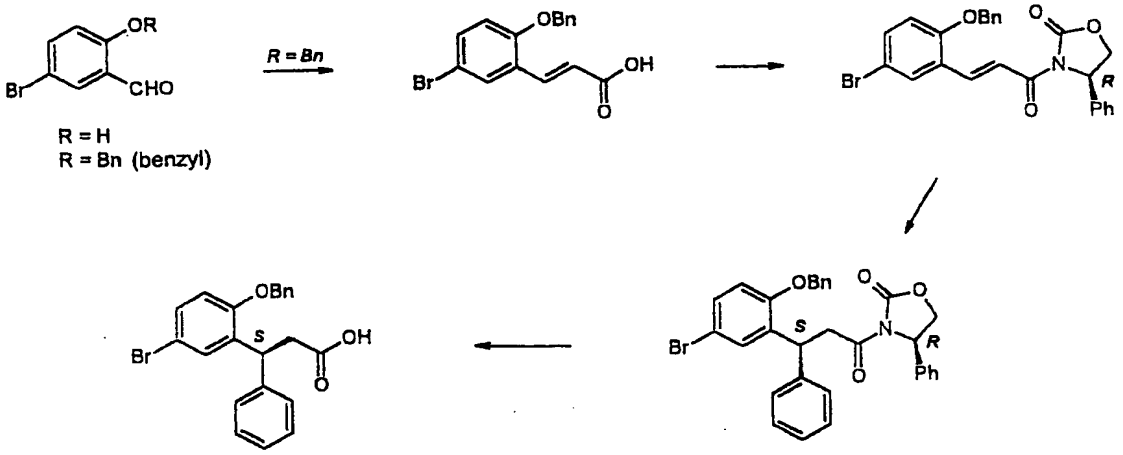
1.2 g (2.0 mmol) of the ephedrinium salt were dissolved in a mixture of acetone (5 ml) and ethanol (10 ml). After treatment with water (0.4 ml) and conc. (37%) aqueous hydrochloric acid (0.34 ml), the solution was evaporated in vacuum, and the residue was redissolved in 1M aqueous hydrochloric acid (2 ml) and dichloromethane (10 ml). The organic phase was separated, washed twice with water (2 ml), and evaporated to dryness to give *R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid* as a colourless oil which slowly solidified (0.4 g, 98% yield), m.p. 105.6°C (from ethyl acetate/n-

heptane); tlc: (7) 0.21; $[\alpha]_D^{20}$ = -21.1 (c = 1.0, ethanol), e.e. 99.9% (HPLC). NMR: identical with the racemic acid.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
The combined mother liquids from the above resolution and recrystallizations were treated under stirring and cooling (18°C) with excess conc. aqueous hydrochloric acid. The precipitate (ephedrinium hydrochloride) was filtered off, and the filtrate was evaporated to dryness. The residue was redissolved in dichloromethane (1.5 litre) and then washed with several portions of 1 M aqueous hydrochloric acid followed by water. After drying (Na_2SO_4), filtration, and evaporation 479 g of crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid were obtained as a yellow viscous oil. The pure S-(+) enantiomeric acid was converted into the 1R,2S-(-)-ephedrine salt as described above for the R-(-) acid. Two recrystallizations from boiling ethanol provided colourless crystals of *S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid 1R,2S-(-)-ephedrinium salt* in 83% yield, m.p. 158.7°C, e.e. 97.8% (HPLC). NMR ($CDCl_3$): 9.47, 30.85, 41.54, 42.92, 61.48, 70.13, 70.30, 113.04, 113.66, 125.89, 126.01, 127.32, 127.84, 128.18, 128.44, 129.83, 130.68, 135.94, 136.63, 140.44, 144.13, 155.19, 178.94.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid was obtained in quantitative yield from this ephedrinium salt by the method described above for the R-(-) acid, tlc: (7) 0.20, e.e. (NMR) > 99%, mp 105.5°C; $[\alpha]_D^{20}$ = +22.6 (c = 1.0, ethanol); NMR: identical with the racemic acid.

b) **Enantioselective Synthesis of R-(-)- and S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid**



2-Benzyloxy-5-bromobenzaldehyde

To a solution of 0.1 mol of 5-bromo-2-benzaldehyde in THF (150 ml) was added 0.1 mol of K_2CO_3 and 0.11 mol of benzyl bromide. The mixture was refluxed for 2 hrs and water (500 ml) was added. After addition of ethyl acetate (400 ml) and stirring the organic layer was washed with water, dried (sodium sulphate) and evaporated to dryness. The resulting slightly yellow solid of pure (tlc) 2-benzyloxy-5-bromo-benzaldehyde was used as such in the next step.

3-(2-Benzyloxy-5-bromophenyl)-acrylic acid

A mixture of 2-benzyloxy-5-bromobenzaldehyde (0.10 mol), malonic acid (15.0 g), and piperidine (2.0 ml) in 150 ml of pyridine was first heated at 90°C for 90 min and subsequently refluxed for 0.5 hrs. After cooling to room temperature, the reaction was poured on a mixture of ice (1 kg) and concentrated aqueous hydrochloric acid (250 ml). The solid

material that precipitated after stirring for 2 hrs. was collected by suction and recrystallized from a minimum of boiling methanol.

3-[3-(2-Benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyl-oxazolidin-2-one

Pivaloylchloride (7 g) was added dropwise at -30°C to a stirred solution of 3-(2-benzyloxy-5-bromophenyl)-acrylic acid (50.0 mmol) and triethylamine (15.0 ml) in 200 ml of tetrahydrofuran. After an additional hour the temperature was lowered to -50°C and (R)-2-phenyloxazolidin-2-one (9.0 g) and lithium chloride (2.5 g) were added in one portion. The cooling bath was then removed and stirring was continued over 18 hrs. The reaction was diluted with water and 3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyloxazolidin-2-one was isolated by extraction with ethyl acetate.

3-[3-(2-Benzyloxy-5-bromophenyl)-(3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one

To a precooled (-30°C) mixture of copper-(I) chloride (21.0 g) and dimethylsulfide (45 ml) in dry tetrahydrofuran (150 ml) was added dropwise an ethereal solution of phenylmagnesiumbromide (0.3 mol). The mixture was stirred 20 min at the same temperature and then cooled to -40°C. A solution of 3-[3-(2-Benzyloxy-5-bromophenyl)-acryloyl]-(4R)-4-phenyl-oxazolidin-2-one (50.0 mmol) in dry tetrahydrofuran (150 ml) was added during 10 min. The cooling bath was removed and stirring was continued for 18 hrs. The mixture was quenched with half-saturated aqueous ammonium chloride solution and the product was isolated by extraction with ethyl acetate.

S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
A solution of the above described 3-[3-(2-benzyloxy-5-bromophenyl)-(3S)-3-phenylpropionyl]-(4R)-4-phenyloxazolidin-2-one in tetrahydrofuran (300 ml) and water (100 ml) was cooled to 0°C and then treated with 30% aqueous hydrogen peroxide (20 ml) followed by solid lithium hydroxide (4.3 g). Water was added after 2 hrs and the chiral auxiliary was removed by extraction with ethyl acetate. The aqueous phase was acidified with aqueous hydrochloric acid (10%) and crude S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was extracted with tert.-butyl-methylether.

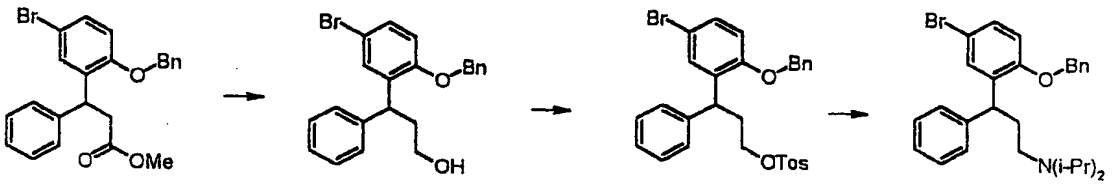
HPLC analysis (Chiralpak AD, mobile phase hexane/2-propanol/trifluoro acetic acid [92:8:0.1, vol/vol-%); flow 1.0 ml/min, detection 285 nm) indicated an enantiomeric ratio 93:7 (retention times 14.8 min and 11.5 min, respectively). The e.e. of 86% of the S-(+) enantiomer can be improved to >98.5% by recrystallization of the diastereomeric salts using "nitromix" (Angew. Chem. Int. Ed. Engl. 1998, Vol. 37, p. 2349) or (1R,2S)-(-)-ephedrine hemihydrate as described above. The S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid was isolated after acidification of aqueous solutions of the diastereomeric salts. It forms colourless crystals which gave an optical rotation of $[\alpha]_D^{22}$ = +21.6 (c = 0.5, MeOH).

R-(-)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionic acid
Conjugate organocuprate addition of phenylmagnesiumbromide to *3-[3-(2-benzyloxy-5-bromophenyl)-acryloyl]-(4S)-4-phenoyloxazolidin-2-one* as described above for the S-(+)enantiomer gave crystalline R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid in an e.e. of 99.6% after two recrystalliza-

tions, $[\alpha]_D^{22}$ = -21.7 (c = 0.5, MeOH).

c) Synthesis of the R- and S- Enantiomers of Intermediate B

(i) Phenylpropanol Route



(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol

A solution of the methyl(±)-propionate (121.0 g) in 350 ml of dry tetrahydrofuran was slowly added under an atmosphere of nitrogen to a suspension of lithium aluminiumhydride (7.9 g) in tetrahydrofuran (350 ml). After stirring at room temperature for 18 hrs, 20% aqueous HCl was added dropwise and the product was isolated by repeated extraction with diethyl ether. The combined extracts were gradually washed with hydrochloric acid, sodium hydroxide solution, distilled water, and then dried (Na_2SO_4) to give a light yellow viscous oil (108.8 g, 96.3% yield) after evaporation which gradually crystallized, m.p. 73.8°C, tlc: (1) 0.47, (±)-3-*(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol*. NMR ($CDCl_3$): 37.52, 39.52, 60.84, 70.54, 113.54, 113.83, 126.29, 127.30, 127.51, 129.99, 128.24, 128.38, 129.99, 130.88, 135.69, 136.40, 143.53, 155.12.

The same product was obtained after reduction of *(±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid* with lithium aluminium hydride in tetrahydrofuran (30 min, 25°C), 31% yield.

(±)-Toluene-4-sulph nic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester

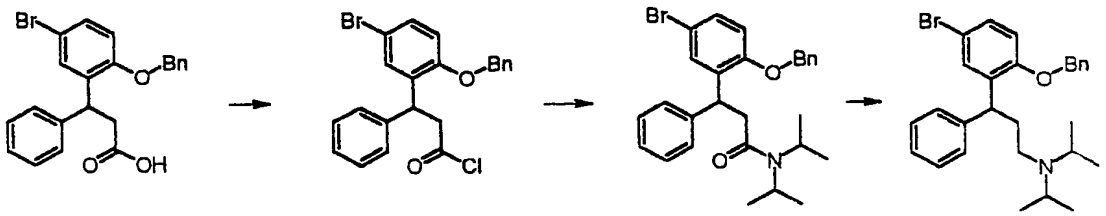
A cooled (5°C) solution of (±)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropan-1-ol (108.0 g) in dichloromethane (300 ml) was treated with pyridine (79.4 ml) and then p-toluenesulphonyl chloride (60.6 g) in dichloromethane (200 ml). After 18 hrs. at room temperature the solvent was removed in vacuum and the residue was extracted with diethyl ether. The extract was washed with hydrochloric acid, water, and dried over anhydrous sodium sulphate to give *(±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester* as a light yellow oil after concentration under reduced pressure (140.3 g, 93.6% yield), tlc: (1) 0.66. NMR ($CDCl_3$): 21.67, 33.67, 39.69, 68.58, 70.28, 113.21, 113.76, 126.47, 127.84, 128.10, 128.25, 128.41, 128.51, 129.81, 130.26, 130.42, 132.91, 134.39, 136.41, 142.16, 155.07.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

A solution of the (±)-toluenesulphonate ((±)-toluene-4-sulphonic acid 3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl ester, 139.3 g) in acetonitrile (230 ml) and N,N-diisopropylamine (256 g) was refluxed for 97 hrs. The reaction mixture was then evaporated to dryness and the residue thus formed was partitioned between diethyl ether (500 ml) and aqueous sodium hydroxide (2 M, 240 ml). The organic phase was washed twice with water (250 ml) and then extracted with 1 M sulphuric acid. The aqueous phase was adjusted to about pH 12-13 and reextracted with ether (500 ml). The organic phase was washed with water, dried (Na_2SO_4) and evaporated to provide *(±)-[3-(2-benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine* as a brown and viscous syrup (94.5 g, 77.9%

yield), tlc: (2) 0.49. NMR ($CDCl_3$): 20.65, 20.70, 36.70, 41.58, 43.78, 48.77, 70.24, 113.52, 126.02, 127.96, 128.20, 128.36, 129.82, 130.69, 136.34, 136.76, 144.20, 155.15.

(ii) Phenylpropionamide Route



S-(+)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropionyl chloride

Thionylchloride (4.5 g, 2.8 ml, 37.8 mmol) and some drops of dimethylformamide were added to a solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid (10.3 g, 25 mmol) in ethyl acetate (60 ml). The mixture was refluxed until tlc control indicated complete consumption of the starting material (2 hrs). Evaporation in vacuum gave the acid chloride as a light yellow liquid in almost quantitative yield (10.7 g). Conversion of an aliquot to the methyl ester showed a single spot in tlc (R_f 0.54, solvent system (7)).

S-(+)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide

A solution of S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenyl-propionyl chloride (9.6 g, 22.3 mmol) in ethyl acetate (40 ml) was added dropwise to a stirred and cooled (3°C) solution of diisopropylamine (6.4 g, 49.0 mmol) in 60 ml of ethyl acetate. The reaction was stirred for 18 hrs at room temper-

ature and then washed with water, aqueous hydrochloric acid (1 M) and half saturated brine. The organic phase was dried (sodium sulphate) and evaporated to dryness. The colourless oily residue (10.7 g, 97% yield) of S-(+)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide showed a single spot on tlc: (R_f 0.70 (4)). NMR ($CDCl_3$): 18.42, 20.46, 20.63, 20.98, 39.51, 41.44, 45.76, 48.63, 70.00, 112.84, 113.64, 126.10, 126.45, 127.34, 127.78, 128.20, 128.36. 129.93, 130.59, 135.18, 136.52, 143.52, 155.17, 169.61.

(±)-N,N-Diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenyl-propionamide

The amide was prepared from diisopropylamine and the racemic acid chloride as described above for the S-(+) enantiomer. The viscous colourless oil was dissolved in ethanol and the solution stored at -30°C. From this solution colourless crystals were obtained, m.p. 101.8°C.

(±)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

To a stirred solution of (±)-N,N-diisopropyl-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionamide (11.8 g) in 40 ml of dry tetrahydrofuran was added 1 M lithium aluminium hydride/tetrahydrofuran (36 ml). The reaction was refluxed for 4 hrs and then quenched with the dropwise addition of water. After removal of the precipitate the solvent was evaporated and the oily residue dissolved in diluted sulphuric acid. The aqueous phase was washed several times with diethyl ether, adjusted to pH 10-12 (aqueous NaOH), and extracted with diethyl ether. The extract was dried (sodium sulphate), filtered and evaporated to dryness in vacuum to leave 8.1 g (76.7%) of the title compound as a viscous colourless oil, tlc:(4) 0.86. The NMR spectrum corresponds to the product, obtained from the

tosylate precursor (see above).

S-(+)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

Repetition of the reaction sequence by using S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave S-(+)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ = +18.5 (c = 10.0, ethanol), e.e. of a representative batch 99.4%

R-(-)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine

Repetition of the reaction sequence by using R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as the starting material gave R-(-)-[3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropyl]-diisopropylamine as a viscous colourless oil, $[\alpha]_D^{22}$ = -17.3 (c = 10.0, ethanol), e.e. of a representative batch 98.3%.

The optical purities were determined by chiral HPLC using Chiralpak OD columns.

(±)-4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride

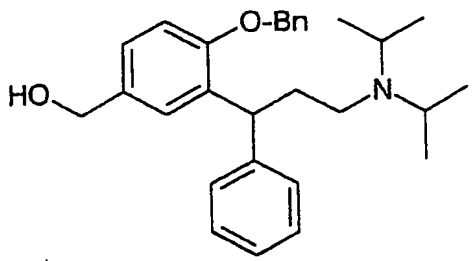
An ethereal Grignard solution, prepared from the above (±)-amine (22.8 g), ethyl bromide (17.4 g) and magnesium (6.1 g) under an atmosphere of nitrogen was diluted with dry tetrahydrofuran (200 ml) and then cooled to -60°C. Powdered solid carbon dioxide (ca. 50 g) was then added in small portions and the green reaction mixture was warmed to room temperature. After the addition of an aqueous solution of ammonium chloride (200 ml, 10%) and adjustment of the aqueous phase to

pH 0.95, a white solid was recovered by filtration to provide *(±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid hydrochloride* (14.7 g, 64.3% yield), m.p. 140°C (dec.), tlc: (2) 0.33. NMR (CD_3OD): 17.07, 18.77, 33.55, 43.27, 56.50, 71.50, 112.89, 124.10, 127.94, 129.07, 129.25, 129.34, 129.59, 129.66, 130.18, 131.60, 132.78, 137.60, 143.30, 161.11, 169.70.

(±)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol

Intermediate A (n = 1)

The (±)-hydrochloride was converted into its methyl ester (MeOH, trace sulphuric acid, 6h reflux) and the free oily base thus obtained (28 g; tlc (2): R_f 0.46) was dissolved in dry diethyl ether (230 ml). This solution was slowly (2h) dropped under a nitrogen atmosphere to a suspension of lithium aluminium hydride (1.8 g) in ether (140 ml). After stirring for 18 hrs, the reaction was quenched by the addition of water (4.7 ml). The organic phase was dried over anhydrous sodium sulphate, filtered and evaporated to dryness to provide *(±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol* (26 g, 98.9% yield), as an oil which gradually crystallized, m.p. 86.4°C, tlc: (2) 0.32. NMR ($CDCl_3$): 20.53, 20.61, 36.87, 41.65, 44.14, 48.82, 65.12, 70.09, 111.80, 125.77, 125.97, 126.94, 127.55, 128.08, 128.37, 128.44, 133.27, 134.05, 134.27, 137.21, 144.84.



Intermediate A

(±)-[4-Benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[C^2H]methanol

Intermediate d_2-A (n = 2)

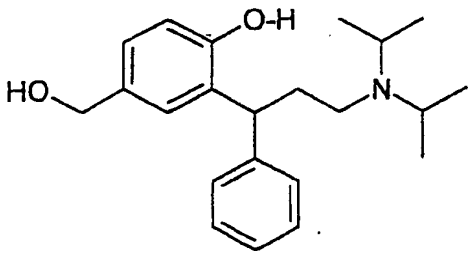
Repetition of the above described reduction of the methyl-ester of *(±)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid* by the use of lithium aluminium deuteride gave (±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-[C^2H]methanol, colourless amorphous solid in 77% yield; tlc: (2) 0.33. NMR ($CDCl_3$): 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centred at 64.96, 70.05, 111.76, 125.72, 127.34, 128.03, 128.32, 128.38, 133.15, 133.99, 137.17, 144.80, 155.52.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Intermediate B (n = 1)

A solution of Intermediate A (9.1 g) in methanol (100 ml) was hydrogenated over Raneynickel (4.5 g) under ambient conditions. After 5 hrs thin layer chromatography indicated complete hydrogenolysis. The catalyst was filtered off and the solution evaporated to dryness to leave an oil (6.95 g, 96.5% yield) which gradually solidified, *(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol*, m.p. 50°C, tlc: (2) 0.15. NMR ($CDCl_3$): 19.42, 19.83, 33.22, 39.62, 42.27, 48.27, 65.19, 118.32, 126.23, 126.55, 127.47, 128.33, 132.50, 144.47, 155.38.

Hydrochloride: colourless crystalls, m.p. 187-190°C (with decomposition)



Intermediate B

S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Hydrogenolysis of *S-(-)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (prepared from S-(+)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 85% yield, colourless solid; m.p. ≥ 50°C, $[\alpha]_D^{22}$ = -19.8 (c = 1.0, ethanol); NMR ($CDCl_3$): 19.58, 19.96, 33.30, 39.52, 42.10, 48.00, 65.40, 118.58, 126.31, 126.57, 127.16, 127.54, 128.57, 132.63, 132.83, 144.55, 155.52.

S-(+) hydrochloride: colourless, non-hygroscopic solid, m.p. 186.4°C (dec.); $[\alpha]_D^{22}$ = +6.6 (c = 0.5, water). NMR (DMSO-d_6): 16.58, 18.17, 31.62, 41.37, 45.90, 54.02, 63.07, 115.18, 126.05, 126.37, 128.03, 128.45, 129.04, 133.12, 143.88, 153.77.

R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Hydrogenolysis of *R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-methanol* (prepared from R-(-)-3-(2-benzyloxy-5-bromophenyl)-3-phenylpropionic acid as described for the racemic series) gave the title compound in 87% yield,

colourless solid; m.p. ≥ 50°C, $[\alpha]_D^{22}$ = +21.3 (c = 1.0, ethanol).

R-(-) hydrochloride: colourless, non-hygroscopic solid, m.p. 179.8°C (dec.); $[\alpha]_D^{22}$ = -7.2 (c = 0.5, water); NMR (DMSO-d_6): 16.59, 18.19, 31.64, 41.38, 45.92, 54.07, 63.08, 115.19, 126.07, 126.39, 128.04, 128.46, 129.05, 133.13, 143.89, 153.79.

S-(+)-mandelate: m.p. 139.7°C, $[\alpha]_D^{21}$ = +38.3 (c = 1.0, ethanol)

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$]methyl-phenol

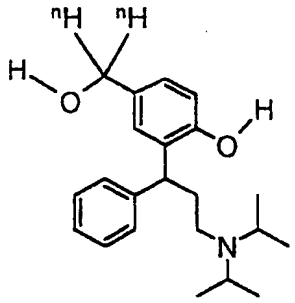
Intermediate d_2-B (n = 2)

A stirred suspension of lithium aluminium deuteride (0.1 g, 2.38 mmol) in 5 ml of dry diethyl ether was treated during 30 min at room temperature under an atmosphere of dry nitrogen with a solution of (±)-4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzoic acid methyl ester (1.0 g, 2.17 mmol) in dry diethyl ether (5 ml). After an additional stirring at room temperature for 18 hrs the reaction was quenched by the dropwise addition of 0.17 ml of ^2H_2O. The resultant precipitation was filtered off, washed with small portions of ether, and the combined organic phases were evaporated to dryness in vacuum to leave

(±)-[4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-phenyl]-[$^2H_2$]methanol

as slightly yellow, viscous oil which gradually crystallized, m.p. 84.1°C; tlc: (2) 0.33 (starting material 0.46), 0.725 g, 77.2% yield. NMR ($CDCl_3$): 20.46, 20.55, 36.77, 41.62, 44.09, 48.77, multiplett centred at 64.30, 70.05, 111.76, 125.72, 125.94, 126.92, 127.34, 127.71, 128.03, 128.32, 128.38, 133.15, 133.99, 137.17, 144.80, 155.52.

A solution of the above (±)-[4-benzyloxy-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]-[$^2H_2$]methanol (0.129 g, 0.29 mmol) in a suspension of methanol (5 ml) and wet Raney-Nickel (0.1-0.2 g) was stirred at room temperature under an atmosphere of deuterium gas ($^2H_2$). After 1 hr tlc indicated complete disappearance of the starting material. The mixture was filtered, evaporated and the residue was redissolved in diethyl ether (5 ml). The solution was washed with water (2 x 5 ml), dried over sodium sulphate, filtered and evaporated to dryness to leave a pale yellow oil, 76.3 mg, in 74.6% yield, which gradually solidified to give a colourless solid of a m.p. range of 46-49°C. Tlc:(4) 0.57 (starting material 0.77). NMR ($CDCl_3$): 19.57, 19,94, 33.33, 39.56, 42.18, 48.07, 48.43, multiplett centred at 64.61, 118.47, 126.29, 126.58, 127.55, 127.94, 128.38, 132.53, 144.53, 155.37. GC-MS (P-CI, ammonia, TMS derivative): 488.43 (100%), 489.56 (70%), 490.56 (31%), 491.57 (8%).



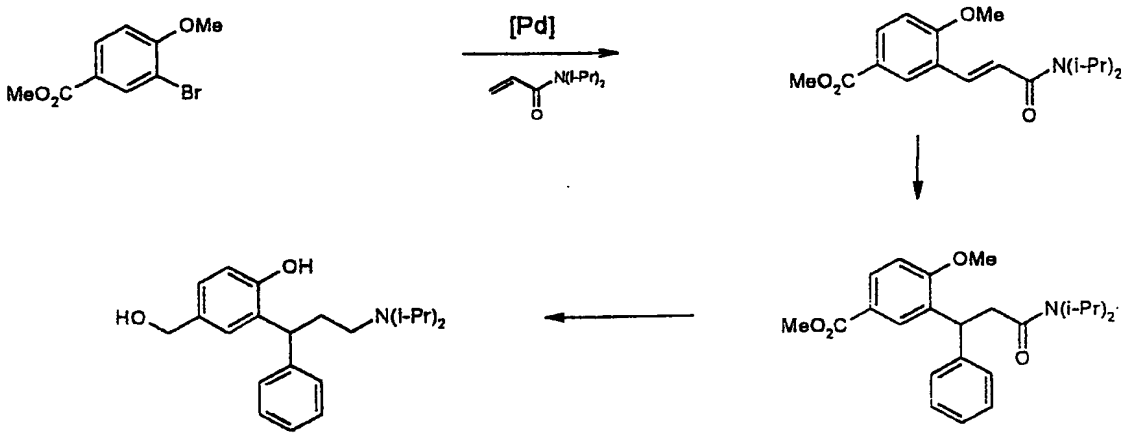
Intermediate d_2-B

n = 2, deuterium

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[$^2H_2$]methyl-phenol

Intermediate d_2-B

(iii) **Heck-Cuprate-Route to Intermediate B**



Intermediate B

N,N-Diisopropyl-acrylamide

A solution of acroyl chloride (42.2 g, 40.6 ml, 0.467 mol) in 125 ml of dichloromethane was slowly added to a cooled (0-5°C) solution of N,N-diisopropylamine in dichloromethane (500 ml). After 2 hrs the precipitated ammonium salt was filtered off and the filtrate was washed with 1M hydrochloric acid (3 x 100 ml), dried (sodium sulphate), and evaporated to dryness. N,N-diisopropyl-acrylamide was obtained as a slight yellow liquid in 48% yield and ca. 99% purity. NMR ($CDCl_3$): 20.54, 21.25, 45.66, 48.10, 125.62, 130.70, 166.17.

(E)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide

((E)-3-(2-Diisopropylcarbamoyl-vinyl)-4-methoxybenzoic acid methyl ester)

The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were

dried before use.

A stirred suspension consisting of N,N-dimethylglycine (6.0 mmol), anhydrous sodium acetate (40 mmol), methyl 3-bromo-4-methoxybenzoate (20 mmol, 4.90 g), N,N-diisopropylacrylamide (24 mmol, 3.72 g), bis-(benzonitrile)-palladium-II chloride (1.5 mol%), and 20 ml of N-methyl-2-pyrrolidinone was heated at 130°C until no starting material could be detected by tlc (starting material methyl 3-bromo-4-methoxybenzoate: R_f 0.73; N,N-diisopropylacrylamide: R_f 0.46; solvent system (1)). After cooling to room temperature 50 ml of an aqueous 2N HCl solution was added. The reaction was diluted with dichloromethane (50 ml) and the precipitated grey palladium metal was filtered off. The organic phase was washed with five portions (50 ml each) of 2N aqueous hydrochloric acid, dried ($MgSO_4$) and evaporated to dryness. The remaining off-white solid was recrystallized from ethyl acetate/n-hexane to give 4.40 g (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide in 69% yield, m.p. 139-140°C, tlc: (1) R_f 0.40.

NMR (CD_2Cl_2): 21.22, 22.10, 46.39, 48.87, 52.59, 56.61, 111.42, 123.39, 123.78, 125.54, 130.32, 132.53, 135.07.

MS (EI, DI, 105°C): 319 ($M^{+\cdot}$, 22), 304 (6%), 276 (8%), 219 (100%), 187 (18%), 160 (7%).

(±)-N,N-Diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide

((±)-3-(2-Diisopropylcarbamoyl-1-phenylethyl)-4-methoxy-benzoic acid methyl ester)

The reaction was carried out under an atmosphere of dry and oxygen-free nitrogen gas. All solvents and reagents were dried before use.

A dark green solution of lithium diphenylcuprate was prepared by addition of phenyllithium solution (12 ml, 24 mmol, cyclo-

hexane/diethyl ether) to a cooled (0°C) and stirred suspension of copper-I bromide dimethylsulphide adduct (2.71 g, 13 mmol) in diethyl ether (40 ml). This solution was cooled to -78°C and then subsequently solutions were added of trimethylchlorosilane (1.5 ml, 12 mmol) in diethyl ether (5 ml) followed by the above cinnamide (3.19 g, 10.0 mmol, (E)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-acrylamide) in 10 ml of tetrahydrofuran. The reaction was stirred for one hour at -78°C, warmed to room temperature and then quenched by the addition of 150 ml of a saturated aqueous solution of ammonium chloride. After 90 min the organic phase was washed with two portions (100 ml) of half saturated aqueous sodium chloride, dried ($MgSO_4$) and evaporated to dryness. The yellow oily residue was dissolved in a minimum of ethyl acetate and purified by column chromatography on silica gel (mobile phase (1)). Evaporation of the combined fractions of the title compound gave

(±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide

as a viscous slightly yellow syrup (1.8 g, 44% yield).
NMR (CD_2Cl_2): 19.45, 19.56, 19.74, 38.86, 44.87, 47.92, 50.80, 54.76, 109.41, 121.32, 125.53, 128.10, 128.43, 128.78, 132.03, 143.20, 159.95, 165.95, 168.87. MS (EI, DI, 105°C): 397 ($M^{+\cdot}$, 41%), 366 (5%), 322 (2%), 269 (3%), 255 (14%), 237 (7%), 165 (5%), 128 (12%), 91 (43%), 58 (100%).

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

A solution of (±)-N,N-diisopropyl-3-(2-methoxy-5-methoxycarbonylphenyl)-3-phenylpropionamide (0.79 g, 2.0 mmol) in 20 ml of tetrahydrofuran was cooled to 5°C and then treated with 2.5 ml of 1M $LiAlH_4$/THF. After stirring at room tem-

perature for 18 hrs. finely powdered aluminium chloride (0.3 g) was added and stirring was continued for additional 4 hrs. The reaction was quenched at 5°C by the dropwise addition of water followed by aqueous sodium hydroxide solution. The mixture was diluted with diethyl ether (150 ml) and the organic phase was washed with half saturated brine, dried (sodium sulphate), and evaporated to dryness to give the title compound as a solid off-white foam. Tlc (2) 0.16, m.p. 48-51°C. A portion of the material was converted into the hydrochloride (ethereal hydrochloric acid), m.p. 186-189°C (dec.).

Hydrogenolytic Deoxygenation of S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

A mixture of *S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol* (683 mg, 2.0 mmol, $[\alpha]_D^{22}$ = -19.8 (c = 1.0, ethanol)), platinium-on-carbon catalyst (120 mg) and acetic acid (1.0 ml) was diluted with ethyl acetate (50 ml) and then hydrogenated at room temperature under a pressure of 4 bar hydrogen gas for 5 hrs. The catalyst was filtered off and the filtrate was evaporated to leave an oil. The residue was redissolved in dichloromethane (25 ml) and the solution was washed with aqueous sodium hydrogencarbonate solution. The organic phase was concentrated to dryness and the oily residue taken up in ethanol (7 ml). Addition of D-(-)-tartaric acid (300 mg) and storage of the clear solution at -25°C gave colourless crystals (310 mg) of **S-(-)-2-(3-diisopropylamino-1-phenylpropyl)-4-methylphenol D-(-) hydrogentartrate** in 33% yield, tlc: (4): 0.66 (starting material 0.31), $[\alpha]_D^{22}$ = -26.7 (c = 1.0, methanol). NMR (CD_3OD): 17.98, 18.37, 20.69, 33.68, 43.12, 56.33, 74.17, 116.31, 127.51, 129.11, 129.50, 129.70, 129.89, 130.41, 144.57, 153.67, 176.88.

A portion of the tartrate was treated with aqueous sodium hydrogencarbonate solution and the free base was isolated in quantitative yield as a colourless oil by extraction with ethyl acetate and evaporation of the extract. $[\alpha]_D^{22}$ = -26.3 (c = 1.0, methanol).

Preferred intermediates in the processes for the preparation of the 3,3-diphenylpropylamines according to the present invention are:
(±)-3-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
R-(-)-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
S-(+)-(2-Benzyloxy-5-bromophenyl)-3-phenylpropanoic acid and its salts,
(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,
S-(-)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol,
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-[C^2H_2]methyl-phenol and their salts.

3. Examples

a) Phenolic monoesters

aa) General procedure

Esters of Carboxylic Acids
A stirred solution of (±)-*2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenol* (Intermediate B, 1.71 g, 5.01 mmol) and acid chloride (5.00 mmol carboxylic acid monochloride for compounds of formula II, 2.50 mmol for compounds

of formula II') in 60 ml of dichloromethane was cooled to 0°C and then triethylamine (0.502 g, 4.96 mmol for compounds of formula II, 1.05 g, 9.92 mmol for compounds of formula II'), dissolved in 10 ml of dichloromethane, was added dropwise during 5-10 min. Stirring was continued for 18 hrs at room temperature, and then the mixture was washed successively with water (25 ml), aqueous sodium hydrogen carbonate (5%, 25 ml), and water (25 ml). The organic phase was then dried (sodium sulphate) and evaporated under reduced pressure and at low temperature. The oily residues thus formed were finally exposed to high vacuum (2-4 hrs.) to remove traces of residual solvents.
The esters of formula II or II' were obtained as colourless to light yellow solids or viscous syrups in purities between 90% and 99% (tlc, HPLC, NMR).

Esters of N-Acylamino Acids

Phenolic Monoesters

To a solution of the respective amino acid (2.0 mmol) in 0.7 ml to 5 ml of N,N-dimethylformamide and 0.5 ml of triethylamine was added at 5°C in one portion methyl chloroformate (2.0 mmol, 288 mg). After stirring for 2 hrs. at the same temperature the cooling bath was removed and a solution of Intermediate B (2.0 mmol, 682 mg) in 5 ml of dichloromethane and triethylamine (0.5 ml) was added. The reaction was allowed to stir for 2-8 hrs and then diluted with diethyl ether (70 ml). Solid precipitates were filtered off and the mixture was washed with aqueous sodium hydrogen sulphate solution (5%) and water. After drying (sodium sulphate), filtration and evaporation in vacuum the residue was purified by flash chromatography on silica gel (eluent: solvent system (4)). N-acylamino acid esters were obtained as viscous oils or waxy solids in yields between 24% and 73%.

bb) Salt formation (Example hydrochloride)

A cooled (0°C) solution of 4.94 mmol amino base in 30 ml of dry diethyl ether was treated under an atmosphere of nitrogen with 4.70 mmol (monoamines of formula II) or 9.4 mmol (diamines of formula II') ethereal (1 M) hydrochloric acid. The oily precipitation was washed repeatedly with dry ether and then evaporated in high vacuum. The residual product solidificated in most cases as an amorphous foam. The highly hygroscopic solids show a wide melting range above 100°C (with decomposition).

The following compounds were prepared according to the method described above and their analytical data are listed below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.47 (4), NMR ($CDCl_3$): 20.36, 20.68, 20.97, 36.59, 42.35, 43.83, 48.76, 64.58, 122.69, 125.61, 126.22, 126.71, 127.96, 128.34, 136.82, 138.97, 143.73, 147.77, 169.24; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 456.8 (100%), 398.4 (4%)

(±)-Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.52 (4); NMR ($CDCl_3$): 20.44, 20.64, 27.67, 36.67, 42.21, 43.87, 48.78, 64.70, 122.71, 125.62, 126.52, 126.78, 127.97, 128.53, 136.86, 138.82, 143.82, 147.86, 172.68; GC-MS/P-CI (ammonia, trimethylsilyl derivative): 470.38 (100%), 398.4 (4%)

(±)-n-Butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4); NMR ($CDCl_3$): 13.77, 18.40, 20.43, 20.51, 20.59, 36.15, 36.82, 42.16,

43.90, 48.83, 49.20, 64.58, 122.66, 125.98, 126.17, 126.74, 127.33, 127.94, 128.33, 136.79, 138.91, 143.82, 171.88; GC-MS/N-Cl (methane, trimethylsilyl derivative): 482.3 (20%), 412.3 (100%), 340.1 (33%), 298.1 (89%), 234.7 (15%); GC-MS/P-Cl (methane, trimethylsilyl derivative): 484.5 (100%), 468.4 (62%), 394.3 (22%); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 484.4 (100%), 398.4 (3%)

(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.43 (4); NMR ($CDCl_3$): 18.99, 19.11, 20.54, 34.21, 36.88, 41.84, 43.91, 48.78, 64.61, 122.54, 125.57, 126.14, 126.81, 127.94, 128.34, 136.84, 138.84, 143.89, 147.85, 175.36

R-(+)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.38 (4), starting material: 0.26; colourless oil (yield 95%); NMR ($CDCl_3$): 19.02, 19.14, 19.96, 20.61, 34.26, 36.92, 41.87, 43.90, 48.80, 64.84, 122.63, 122.63, 125.64, 126.19, 126.92, 127.98, 128.39, 136.96, 138,76, 143.93, 147.97, 175.39.
Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ = +5.5 (c = 1.0, chloroform); NMR ($CDCl_3$): 17.03, 17.53, 18.30, 18.52, 18.95, 19.12, 31.23, 34.10, 41.69, 45.40, 54.22, 54.47, 64.00, 122.32, 126.62, 126.81, 127.40, 128.06, 128.70, 133.88, 140.64, 142.25, 147.81, 175.89.

(±)-2,2-Dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.49 (1); NMR ($CDCl_3$): 20.46, 20.66, 26.53, 27.34, 37.12, 39.21, 41.46, 43.98, 48.81, 64.65, 122.42, 125.58, 126.16, 126.92, 128.37, 134.27, 136.92, 138.82, 143.97, 148.02, 176.97; GC-MS/P-CI

(ammonia, trimethylsilyl derivative): 498.8 (100%), 482.5 (10%), 398.4 (4%)

(±)-2-Acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
((±)-2-[Diisopropylamino)-1-phenylpropyl]-4-(hydroxymethyl)phenyl 2-(acetylamino)acetate)
NMR (CD_3OD): 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171.47, 173,82

(±)-Cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.66 (4), starting material Intermediate B (0.50), colourless oil, yield: 82%. NMR ($CDCl_3$): 20.42, 25.87, 30.25, 36.57, 41.89, 43.97, 47.15, 49.02, 64.63, 122.56, 125.60, 126.16, 126.81, 127.60, 127.94, 128.35, 128.77, 136.74, 138.88, 143.85, 147.92, 175.05.

(±)-Cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.67 (4), starting material Intermediate B (0.50), colourless oil, yield: 93%. NMR ($CDCl_3$): 20.27, 25.40, 25.74, 29.03, 29.16, 36.29, 41.82, 43.31, 44.08, 49.36, 64.62, 122.56, 125.68, 126.22, 126.92, 127.92, 128.38, 136.65, 139.00, 143.72, 147.86, 174.40.
(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.31 (4); colourless syrup (99% yield, purity > 95%);gradually crystallized upon refrigeration; NMR ($CDCl_3$): 20.41, 20.51, 36.65, 42.42, 43.85, 48.79, 64.70, 122.79, 125.74, 126.17, 126.83, 128.13, 128.28, 128.58, 129.48, 130.25, 133.62, 137.21, 139.10, 143.67, 148.00, 164.99.

*R-(+)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-*hydroxymethylphenyl ester
tlc R_f 0.30 (4); colourless syrup
Hydrochloride: colourless amorphous solid; $[\alpha]_D^{20}$ = +14.9 (c = 1.0, chloroform);
NMR ($CDCl_3$): 17.06, 17.53, 18.25, 18.61, 31.23, 42.19, 45.49, 54.26, 54.53, 64.09, 122.55, 126.77, 127.13, 127.58, 128.10, 128.50, 128.72, 128.78, 129.02, 130.17, 133.96, 134.27, 140.81, 142.13, 147.91, 165.40.

(±)-4-Methylbenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.30 (4), starting material Intermediate B: 0.24; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$): 20.32, 20.50, 21.78, 36.13, 42.35, 43.98, 49.29, 64.66, 122.79, 125.81, 126.19, 126.70, 127.04, 128.30, 129.32, 129.76, 130.29, 136.94, 139.20, 143.61, 144.46, 148.04, 165.07.
LC-MS: 459 ($M^{+\cdot}$, 3.5%), 444 (17%), 223 (2.5%), 195 (2%), 119 (48%), 114 (100%).

(±)-2-Methylbenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
viscous colourless oil, tlc: (4) 0.64 (starting material R_f 0.51), yield 84%. NMR ($CDCl_3$): 20.44, 20.53, 21.86, 22.01, 36.74, 42.36, 43.87, 48.81, 64.76, 122.93, 123.11, 125.71, 126.12, 126.88, 128.10, 128.48, 130.76, 131.26, 131.70, 132.03, 132.79, 137.28, 139.00, 141,73, 143.72, 148.04, 165.25. LC-MS: 459 ($M^{+\cdot}$, 21%), 444 (100%), 326 (1%), 223 (10%), 213 (6%), 195 (9%), 165 (14%), 115 (94%), 91 (99%).

(±)-2-Acetoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
colourless syrup, tlc: (4) 0.47 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$): 20.39, 20.57, 20.96, 36.92, 42.29, 43.88, 48.87, 64.64, 122.39, 122.64, 124.05, 125.80, 126.11, 126.75, 128.09, 128.32, 132.23, 134.66, 137.27, 139.32, 143.64, 147.63, 151.37, 162.72, 169.73. LC-MS: 503 ($M^{+\cdot}$, 7%), 488 (59%), 446 (6%), 326 (22%), 223 (9%), 213 (9%), 195 (9%), 163 (14%), 121 (100%), 114 (88%).

(±)-1-Naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
colourless viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 82%. NMR ($CDCl_3$): 20.46, 20.58, 36.82, 42.46, 43.89, 48.76, 64.81, 122.98, 124.51, 125.64, 125.79, 125.98, 126.15, 126.44, 126.94, 128.12, 128.36, 128.65, 131.37, 131.82, 133.98, 134.45, 137.44, 139.08, 143.73, 148.13, 165.49. LC-MS: 495 ($M^{+\cdot}$, 8%), 480 (100%), 213 (7%), 165 (8%), 155 (95%), 127 (100%), 114 (90%).

(±)-2-Naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
colourless slightly yellow viscous oil, tlc: (4) 0.57 (starting material R_f 0.51), yield 71%. NMR ($CDCl_3$): 20.47, 20.59, 36.71, 42.59, 43.85, 48.81, 64.82, 122.89, 126.89, 127.89, 128.19, 128.41, 128.68, 129.50, 132.03, 132.55, 135.87, 137.22, 139.08, 143.83, 148.20, 165.14. LC-MS: 495 ($M^{+\cdot}$, 7%), 480 (98%), 223 (8%), 213 (6%), 195 (6%), 165 (8%), 155 (96%), 127 (100%), 114 (81%).

(±)-4-Chlorobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.54 (4), starting material Intermediate B: 0.44; yield: quantitative, viscous light yellow oil; NMR ($CDCl_3$): 20.34, 20.50, 36.41, 42.51, 43.84, 48.93, 64.66, 122.72, 125.82, 126.88, 127.27, 128.06, 128.56, 128.96, 131.60, 133.80, 136.95, 139.30, 140.16, 143.60, 147.87, 164.10. LC-MS: 479 ($M^{+\cdot}$, 1.5%), 464 (10%), 223 (2%), 195 (2%), 165 (1.5%), 139 (25%), 114 (100%).

(±)-4-Methoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.47 (4), starting material Intermediate B: 0.42; yield: 89%, viscous light yellow oil; NMR ($CDCl_3$): 20.31, 20.47, 36.43, 42.39, 43.90, 48.97, 55.53, 64.71, 121.79, 122.86, 125.72, 126.14, 126.79, 128.11, 128.27, 131.27, 131.77, 132.36, 132.84, 137.15, 139.01, 143.74, 148.08, 163.92, 164.71. LC-MS: 475 ($M^{+\cdot}$, 3.5%), 460 (20%), 223 (2%), 195 (2%), 135 (48%), 114 (100%).

(±)-2-Methoxybenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester

Tlc: R_f 0.40 (4), starting material Intermediate B: 0.42; yield: 98%, viscous light yellow oil; NMR ($CDCl_3$): 20.29, 20.42, 36.50, 41.92, 44.02, 49.09, 55.95, 64.72, 119.10, 120.20, 122.86, 125.64, 126.10, 126.82, 128.06, 128.30, 132.38, 134.32, 137.11, 139.01, 143.87, 148.00, 159.82, 164.40. LC-MS: 475 ($M^{+\cdot}$, 3.5%), 460 (18%), 223 (1%), 195 (1%), 135 (49%), 114 (100%).

(±)-4-Nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.44 (4), starting material Intermediate B: 0.42; yield: 78%, viscous yellow oil which slowly solidified; m.p. 123.6°C; NMR ($CDCl_3$): 20.47, 20.62, 36.52, 42.66, 43.70, 48.75, 64.69, 122.61, 123.72, 125.91, 126.33, 127.04, 128.02, 128.37, 131.32, 134.86, 136.83, 139.55, 143.56, 147.75, 150.93, 163.04. LC-MS: 490 ($M^{+\cdot}$, 1.5%), 475 (15%), 327 (0.8%), 223 (3%), 195 (3%), 150 (15%), 114 (100%).

(±)-2-Nitrobenzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester
Tlc: R_f 0.32 (4), starting material Intermediate B: 0.42; yield: 92%, viscous yellow oil which slowly solidified; NMR ($CDCl_3$): 20.39, 20.50, 36.74, 42.14, 43.89, 48.71, 48.92, 64.59, 122.15, 123.95, 124.18, 125.89, 126.25, 127.23, 127.99, 128.39, 129.95, 132.95, 133.08, 136.72, 139.62, 143.64, 147.63, 148.15, 163.90. LC-MS: 490 ($M^{+\cdot}$, 1%), 475 (11%), 327 (2.5%), 223 (2.5%), 195 (3%), 165 (3%), 150 (7%), 114 (100%).

(±)-N-Acetylglycine 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester/(±)-2-Acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ((±)-2-[Diisopropylamino-1-phenylpropyl]-4-(hydroxymethyl)-phenyl 2-(acetylamino)acetate)
NMR (CD_3OD): 20.33, 20.61, 22.17, 30.54, 42.39, 48.62, 51.04, 64.88, 117.99, 124.73, 125.51, 127.01, 127.75, 129.31, 131.63, 137.33, 146.67, 147.43, 171,47, 173.82.

(±)-Malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.38 (4); NMR ($CDCl_3$): 20.52, 20.62, 20.69, 36.95, 41.84, 42.82, 43.89, 48.23,

64.83, 123.37, 127.36, 127.97, 128.42, 128.38, 129.06, 131.55, 137.50, 138.90, 148.23, 148.32, 160.54

(±)-Succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.40 (4); NMR ($CDCl_3$): 20.54, 20.63, 20.73, 30.69, 36.91, 41.80, 43.92, 48.20, 64.81, 122.60, 127.41, 127.93, 128.39, 129.31, 131.80, 136.73, 138.92, 143.82, 148.17, 168.01

(±)-Pentanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$): 20.47, 20.60, 32.87, 36.93, 41.82, 43.90, 48.22, 64.81, 64.83, 122.85, 127.39, 127.99, 128.35, 129.31, 131.84, 136.98, 138.94, 143.80, 147.40, 169.05

(±)-Hexanedioic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl]ester, tlc: R_f 0.43; NMR ($CDCl_3$): 20.64, 23.40, 34.37, 36.95, 41.84, 43.88, 48.25, 64.87, 122.88, 127.34, 127.97, 128.39, 129.33, 131.80, 136.99, 138.94, 143.82, 147.65, 168.72

b) Identical diesters

(±)-Identical diesters (formula III) were prepared and worked up as described above with the exception that 2.4 mmol of both triethylamine and acyl chloride (R^1-COCl) were used. The physical properties were similar to the bases and salts described above.
Diesters of N-acylaminoacids were prepared as described for phenolic monoesters with the exception that an additional molar equivalent of acylating agent (mixed acid anhydride) was used.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.65 (4). This diester was prepared from mixed formic acetic anhydride and Intermediate B as described for other substrates previously (F. Reber, A. Lardon, T. Reichstein, *Helv. Chim. Acta* **37**: 45-58 [1954])

(±)-Acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester, tlc: R_f 0.76 (4); GC-MS/P-CI (ammonia): 426.3 (100%), 368.3 (22%); GC-MS/P-CI (methane, trimethyl-silyl derivative): 426.4 (64%), 410.3 (16%), 366.3 (100%); hydrochloride, NMR ($DMSOd_6$)- 16.50, 16.76, 18.05, 20.94, 21.04, 27.02, 31.39, 41.28, 45.26, 53.80, 65.21, 123.39, 126.84, 127.61, 127.85, 128.70, 134.41, 135.49, 142.68, 148.20, 169.32, 170.42

(±)-Propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester, tlc: R_f 0.82 (4); NMR ($CDCl_3$): 20.53, 20.73, 21.14, 27.66, 36.73, 42.10, 43.68, 48.65, 65.75, 122.65, 126.10, 127.01, 127.70, 128.34, 128.78, 133.73, 136.81, 143.76, 148.45, 172.45, 174.21; GC-MS/P-CI (ammonia): 454.8 (100%), 438.5 (9%), 382.4 (27%)

(±)-n-Butyric acid 4-n-butyryloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.86 (4); NMR ($CDCl_3$): 13.70, 13.76, 18.44, 20.53, 20.69, 21.13, 36.14, 36.76, 37.09, 42.08, 43.73, 48.71, 65.64, 122.81, 125.97, 126.97, 127.92, 128.35, 128.77, 133.78, 136.99, 143.76,

148.41, 171.68, 173.40; GC-MS/P-CI (ammonia): 482.8 (100%), 396.4 (67%)

(±)-Isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester, tlc: R_f 0.83 (4), NMR ($CDCl_3$): 18.97, 19.10, 20.64, 20.67, 34.01, 34.23, 36.98, 41.72, 43.70, 48.65, 65.61, 122.50, 126.18, 126.73, 127.92, 128.13, 128.36, 133.90, 137.01, 143.85, 148.41, 175.17, 176.81; GC-MS/N-CI (methane): 480.3 (15%); GC-MS/P-CI (methane): 482.5 (63%), 466.4 (18%), 394.3 (100%)

(±)-2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethylpropionyloxy)-benzyl ester, Tlc: R_f 0.96 (4); NMR ($CDCl_3$): 20.44, 20.75, 27.09, 27.24, 37.18, 38.68, 39.15, 41.25, 43.66, 48.20, 65.50, 122.36, 126.32, 127.22, 127.48, 127.83, 128.29, 133.99, 136.98, 143.87, 148.37, 176.70, 178.10; GC-MS/P-CI (methane): 510.5 (76%), 494.5 (21%), 408.4 (100%)

(±)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.80 (4); NMR ($CDCl_3$): 20.62, 36.95, 41.72, 43.89, 48.23, 66.76, 122.22, 125.33, 127.36, 127.62, 127.89, 127.89, 127.97, 128.38, 129.49, 130.52, 130.64, 131.15, 131.22, 131.98, 136.38, 137.66, 143.82, 148.95, 164.77, 166.60

(+)-Benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester

Hydrochloride: colourless solid; tlc: (4) 0.70, $[\alpha]_D^{20}$ = +24.2 (c = 1.0, chloroform). NMR (DMSO-d_6): 16.52, 17.99, 18.06, 26.99, 31.32, 53.94, 65.98, 123.58, 127.65, 127.98, 128.62, 128.90, 129.02, 129.45, 129.71, 130.10, 133.64, 134.32, 134.55, 135.60, 142.52, 148.37, 164.53, 165.76.

c) Mixed diesters

Mixed diesters (formula IV) were prepared by acylation of the respective benzylic or phenolic monoesters. Working up and physical properties corresponded to the bases and salts described above.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.76 (4); NMR ($CDCl_3$): 20.62, 20.91, 33.25, 42.20, 42.28, 48.23, 70.70, 122.96, 127.36, 127.97, 128.38, 128.73, 132.02, 135.41, 137.11, 143.81, 149.35, 161.34, 168.95

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester, tlc: R_f 0.74 (4); NMR ($CDCl_3$): 20.60, 36.93, 41.72, 43.89, 48.23, 70.71, 122.50, 125.33, 127.30, 127.89, 127.97, 128.36, 129.57, 130.65, 131.13, 132.05, 135.41, 136.66, 143.80, 149.15, 161.35, 164.78

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester
Viscous colourless oil, tlc: R_f 0.70 (4); NMR ($CDCl_3$): identical with R-(+) enantiomer, see below.

R-(+)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester
tlc: R_f 0.70 (4)
Hydrochloride: colourless non-hygroscopic solid $[\alpha]_D^{20}$ = +27.1 (c = 1.0, chloroform). NMR ($CDCl_3$): 17.14, 18.53,

21.04, 31.51, 42.25, 46.27, 54.74, 65.58, 123.18, 127.07, 127.55, 127.61, 127.99, 128.80, 130.22, 134.14, 134.81, 135.27, 141.44, 148.54, 165.19, 170.81.

(±)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 18.99, 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 126.76, 127.14, 127.94, 128.39, 128.84, 133.55, 137.04, 143.84, 148.56, 170.84, 175.18

(+)-Isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester
colourless oil
Hydrochloride: colourless hygroscopic solid; $[\alpha]_D^{20}$ = +14.6 (c = 1.0, chloroform); NMR ($CDCl_3$): 16.89, 17.04, 18.31, 18.54, 18.92, 19.06, 20.95, 31.49, 34.07, 41.64, 46.17, 54.55, 65.49, 122.91, 126.93, 127.48, 127.83, 128.74, 134.50, 134.88, 141.61, 148.44, 170.67, 175.63.

(±)-2,2-Dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.80 (4); NMR ($CDCl_3$): 20.63, 20.93, 27.19, 33.25, 37.49, 42.21, 42.25, 48.22, 67.37, 123.18, 127.36, 127.84, 128.39, 131.16, 137.34, 143.84, 148.29, 168.93, 178.40

(±)-2,2-Dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, tlc: R_f 0.81 (4); NMR ($CDCl_3$): 20.60, 20.79, 27.09, 36.93, 37.35, 41.85, 42.29, 48.25, 65.91, 122.36, 127.37, 127.99, 128.39, 129.38, 132.69, 136.00, 136.85, 143.80, 170.45, 176.60

d) Benzylic monoesters

A mixture consisting of Intermediate B (80 mg, 0.23 mmol), vinyl ester (0.4 ml), tert.-butyl methylether (18 ml), and lipase enzyme (1.0 g) was gently shaken at room temperature. Benzylic formate, acetate, and n-butyrate were prepared from the corresponding vinyl ester donors using SAM I lipase (Amano Pharmaceutical Co.). Benzoylation was achieved with vinyl benzoate in the presence of Lipozym IM 20 (Novo Nordisk), whereas pivalates and isobutyrates were obtained from the corresponding vinyl esters under catalysis of Novozym SP 435 (Novo Nordisk). Tlc analysis indicated after 2 - 24 hrs complete disappearence of the starting material (R_f = 0.45 (3)). The mixture was filtered and then evaporated under high vacuum (< 40°C) to give the carboxylic acid (R^1-CO_2H) salts of the respective benzylic monoesters as colourless to light yellow oils.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-Formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.25 (2); NMR ($CDCl_3$): 19.43, 33.24, 39.61, 42.25, 48.21, 68.44, 118.09, 127.34, 127.66, 128.31, 128.39, 133.97, 144.47, 156.63, 161.32

(±)-Acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.26 (2); NMR ($CDCl_3$): 19.45, 20.96, 33.26, 39.63, 42.27, 48.23, 63.59, 118.00, 127.36, 128.33, 128.48, 128.53, 129.13, 131.59, 133.88, 144.49, 155.74, 170.44

(±)-Propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.45 (2); NMR ($CDCl_3$): 19.02, 19.43, 27.58, 33.20, 39.61, 42.25, 48.21, 64.08, 118.30, 125.30, 127.03, 127.39, 128.31, 130.12, 134.22, 144.51, 155.64, 173.22

(±)-Butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.54 (2); NMR ($CDCl_3$): 13.58, 18.40, 19.45, 33.29, 35.88, 39.65, 42.23, 48.25, 63.96, 118.32, 124.55, 126.20, 127.35, 128.32, 129.91, 134.22, 144.50, 155.60, 169.05

(±)-Isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.56 (4); NMR ($CDCl_3$): 19.09, 19.45, 33.28, 33.59, 39.65, 42.29, 48.25, 64.63, 118.35, 125.35, 127.03, 127.38, 128.35, 128.49, 129.79, 134.22, 144.52, 155.65, 175.48

(±)-2,2-Dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.61 (4); NMR ($CDCl_3$): 19.41, 27.15, 33.24, 37.46, 39.61, 42.25, 48.21, 65.10, 118.30, 125.32, 127.00, 127.34, 128.31, 129.42, 134.18, 144.47, 155.61, 178.39

(±)-Benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 18.01, 19.40, 33.24, 39.60, 42.40, 48.20, 66.93, 117.13, 127.18, 127.81, 128.33, 129.98, 130.17, 132.96, 133.58, 142.33, 156.95, 166.60

e) Ethers and silyl ethers

A mixture of Intermediate B (3.4 g, 10 mmol), methanesulphonic acid (2 ml, 31 mmol), and alcohol R^{10}-OH (50-150 ml) was stirred at room temperature until no starting material was detectable (2-24 hrs). After evaporation to dryness (< 35°C) the residue was redissolved in aqueous sodium hydrogen carbonate solution (100-200 ml, 5%, w/v) and the solution was extracted with ethyl acetate (75 ml). The organic phase was separated, dried (Na_2SO_4), filtered and evaporated to give bases of formula VI (R^{11} = H) as colourless to light yellow oils.

Mixed ester ether derivatives, e.g. of Intermediate A, were prepared by benzylic acylation of phenolic ethers, such as Intermediate A, according to the procedure described for examples of the structure of formula IV.

Hydrochlorides:

Molar equivalents of bases of formula VI (R^{11} = H), dissolved in tert.-butyl methylether, and ethereal hydrochloric acid were combined at room temperature. Oily precipitates were separated and dried in vacuum, crystalline hydrochlorides were isolated and recrystallized from acetonitrile or acetone to give colourless crystalline material.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol, tlc: R_f 0.61 (4); GC-MS/P-CI (methane, trimethylsilyl

derivative): 428.4 (100%), 412.3 (49%), 396.3 (52%);
hydrochloride: amorphous hygroscopic colourless solid;
m.p. 161°C; NMR (CD_3OD): 17.39/18.75 (broad signals), 33.79, 43.13, 56.47, 58.00, 75.59, 116.19, 120.79, 127.62, 129.04, 129.14, 129.42, 129.55, 130.43, 144.32, 155.85

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethyl-phenol, tlc: R_f 0.72 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 444.8 (100%), 398.4 (6%);
hydrochloride: colourless non-hygroscopic crystals, m.p. 158-161°C, NMR (CD_3OD): 15.43, 17.12, 18.82, 33.80, 56.49, 66.49, 73.62, 116.19, 127.63, 128.99, 129.13, 129.36, 129.55, 130.58, 130.75, 144.32, 155.77

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-propoxymethyl-phenol, NMR ($CDCl_3$): 18.62, 19.44, 23.10, 33.24, 39.61, 42.26, 48.22, 71.87, 73.94, 117.78, 124.95, 127.35, 127.57, 128.32, 128.47, 133.66, 134.23, 144.48, 155.25

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-isopropoxymethyl-phenol, NMR ($CDCl_3$): 19.44, 22.32, 33.27, 39.65, 42.29, 48.25, 69.28, 72.10, 117.90, 127.38, 128.03, 128.41, 131.10, 133.76, 134.37, 144.51, 154.65.
Hydrochloride: colourless crystals, m.p. 140.4°C, tlc (4) 0.61. LC-MS: 383 (6%, $[M-HCl]^{+\cdot}$), 368 (11%), 324 (1%), 223 (6%), 195 (3%), 165 (2%), 155 (5%), 114 (100%). NMR (DMSO-d_6): 16.57, 18.09, 18.19, 22.29, 31.58, 41.25, 45.87, 53.97, 69.26, 69.92, 115.28, 126.34, 127.08, 127.25, 127.96, 128.45, 129.07, 129.70, 132.31, 143.88, 154.22.

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-butoxymethyl-phenol, NMR ($CDCl_3$): 13.75, 19.44, 19.75, 32.24, 33.28,

39.60, 42.20, 48.20, 72.45, 117.87, 125.50, 127.29, 128.39, 133.70, 134.30, 144.47, 155.36

(±)-Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester, NMR ($CDCl_3$): 19.99, 20.62, 20.90, 33.33, 42.30, 48.21, 58.41, 75.94, 122.92, 127.37, 127.95, 128,35 131.85, 136.99, 138.81, 143.88, 147.88, 168.95

(±)-Acetic acid 2-(3-Diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester, NMR ($CDCl_3$): 15.49, 19.94, 20.95, 33.23, 42.25, 48.25, 65.70, 73.73, 122.63, 127.46, 127.95, 128.36, 131.65, 136.79, 139.71, 143.80, 147.66, 168.99

(±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxymethylphenol, NMR ($CDCl_3$): 0.10, 19.40, 19.43, 33.25, 39.65, 42.25, 48.20, 64.93, 117.90, 124.90, 126.60, 127.35, 128.35, 128.48, 133.80, 137.15, 144.49, 155.28

(±)-Diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-trimethylsilanyloxymethylphenyl)-propyl]amine, NMR ($CDCl_3$): 0.10, 0.29, 19.40, 19.53, 33.28, 41.19, 42.27, 48.25, 66.40, 121.37, 127.36, 128.25, 128.50, 136.42, 144.10, 154.98

(±)-[3-(3-Diisopropylamino-1-phenylpropyl)-4-trimethylsilanyloxyphenyl]methanol, NMR ($CDCl_3$): 0.29, 0.33, 19.40, 19.53, 33.27, 41.16, 42.27, 48.23, 65.22, 118.04, 124.99, 126.52, 127.30, 128.25, 134.16, 136.80, 144.14, 155.06

(±)-Diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyloxyphenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$): 0.28, 0.32, 19.39, 19.43, 33.28, 41.22, 42.33, 48.19, 58.40, 75.95, 117.68, 124.92, 126.60, 127.35, 128.25, 128.55, 134.00, 136.47, 144.16, 155.09

(±)-Diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyloxy-phenyl)-3-phenylpropyl]amine, NMR ($CDCl_3$): 0.28, 0.31, 15.50, 19.42, 19.58, 33.29, 41.17, 42.25, 48.20, 65.70, 72.48, 117.50, 124.75, 126.39, 127.39, 128.25, 128.50, 134.99, 136.28, 144.19, 154.28

(±)-[4-(tert.-Butyl-dimethylsilanyloxy)-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]methanol, R_f 0.65 (3)

(±)-Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, NMR ($CDCl_3$): -4.92, -5.00, 19.40, 19.49, 20.40, 20.83, 23.49, 33.25, 41.22, 42.25, 48.25, 72.55, 81.55, 121.24, 124.88, 127.40, 128.26, 128.44, 128.48, 133.37, 135.74, 144.11, 155.20

(±)-4-(tert.-Butyl-dimethylsilanyloxymethyl)-2-(3-diiso-propylamino-1-phenylpropyl)-phenol, tlc: R_f 0.70 (3); GC-MS/N-CI (methane, trimethylsilyl derivative): 526.5 (59%), 454.3 (100%), 412.2 (14%), 340.1 (42%); GC-MS/P-CI (methane, trimethylsilyl derivative): 528.6 (100%), 512.5 (85%), 470.43 (10%), 396.3 (31%)

(±)-Acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester, NMR ($CDCl_3$): -4.77, -4.88, 19.15, 20.65, 20.93, 24.77, 33.25, 42.20, 48.20, 67.90, 122.79, 125.15, 127.44, 127.90, 128.41, 136.99, 140.55, 143.85, 147.86, 168.95

(±)-{3-[2-(tert.-Butyl-dimethylsilanyloxy)-5-(tert.-butyl-di-methylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropyl-amine, tlc: R_f 0.94 (3); GC-MS/N-CI (methane): 568.6 (62%), 454.3 (100%), 438.2 (10%), 340.2 (58%), 324.8 (16%), 234.7

(78%); GC-MS/P-CI (methane): 570.6 (70%), 554.5 (52%), 512.5 (18%), 438.4 (24%)

(±)-Acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester, tlc: R_f 0.56 (5); GC-MS/P-CI (ammonia): 474.4 (100%), 416.4 (54%); NMR ($CDCl_3$): 20.44, 20.56, 21.07, 36.73, 41.53, 44.01, 48.79, 66.43, 70.00, 111.61, 125.75, 127.34, 127.55, 127.76, 127.90, 128.03, 128.27, 128.39, 133.98, 136.98, 144.63, 156.05, 170.94

(±)-Benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester, tlc: R_f 0.87 (4); NMR ($CDCl_3$): 20.54, 20.60, 36.80, 41.51, 43.95, 48.67, 66.83, 70.04, 111.66, 125.76, 127.35, 127.45, 127.78, 128.06, 128.27, 128.30, 128.42, 128.85, 129.66, 130.55, 132.86, 134.05, 137.03, 144.75, 156.08, 166.46; GC-MS/P-CI (ammonia): 536.5 (100%), 416.4 (42%)

(±)-Isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester, tlc: R_f 0.77 (4); NMR ($CDCl_3$): 19.01, 20.62, 20.65, 34.04, 36.85, 41.54, 43.97, 48.71, 66.15, 70.06, 111.62, 125.79, 125.96, 126.97, 127.24, 127.55, 127.81, 128.08, 128.34, 128.45, 134.05, 137.10, 144.79, 156.00, 177.01; GC-MS/P-CI (ammonia): 502.4 (100%), 416.4 (49%)

f) Carbamates and carbonates

Mono N-substituted carbamates

A solution of 4.0 mmol of Intermediate B, benzylic ether (formula VI, R^{11} = H) or monoester of formula II in dichloromethane (20 ml) was treated at room temperature for 16 hrs with isocyanate (4.8 mmol) or diisocyanate (2.2 mmol). After

washing with 10 ml aqueous sodium hydrogen carbonate (5%, w/v), drying (Na_2SO_4) and evaporation oily residues or colourless solids of the free bases were obtained.

N-disubstituted carbamates

N,N-dialkyl-carbamoylchloride (4.4 mmol) was dissolved in dichloromethane and dropped into a cooled (0°C) and stirred mixture consisting of Intermediate B (4.0 mmol), dichloromethane (30 ml) and triethylamine (7.0 mmol, 0.71 mg, 1 ml). Stirring was continued for 6 hrs. The mixture was then washed with 5 portions (10 ml) of aqueous sodium hydrogen carbonate, dried (sodium sulphate), filtered and evaporated to give the carbamates as colourless oils or solids.

Bis-carbamates were prepared in like manner using Intermediate B and excess isocyanate (4.8 mmol) and toluene as solvent at 65°C over 18 hrs.
Carbonates were prepared and worked-up according to the methods described for the preparation of compounds of formulae II to IV. Alkyl chloroformates were used as acylation reagents.

Hydrochlorides:

The oils or solids were redissolved in tetrahydrofuran (10 ml). Addition of ethereal hydrochloric acid and evaporation to dryness in high vacuum gave crystalline or amorphous carbamate hydrochlorides.

In particular, the following compounds were prepared and their analytical data are given below:

(±)-N-Ethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester, tlc: R_f 0.38 (4); GC-MS/P-CI (ammonia, trimethylsilyl derivative): 486.8 (100%), 413.4 (5%), 398.4 (6%); hydrochloride: m.p. 64°C (with decomposition); NMR (DMSO-d_6): 15.16, 16.68, 18.05, 18.13, 25.33, 31.26, 35.46, 53.94, 62.65, 67.22, 123.04, 125.70, 126.72, 127.86, 128.67, 135.42, 136.02, 140.07, 142.98, 147.53, 154.52

(±)-N,N-Dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
NMR ($CDCl_3$): 20.34, 20.66, 30.51, 36.33, 36.77, 42.00, 48.28, 50.21, 65.65, 119.83, 123.44, 125.19, 126.60, 127.38, 127.54, 129.31, 136.62, 143.33, 150.99, 155.67.

(±)-N,N-Diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
NMR ($CDCl_3$): 20.54, 20.66, 30.49, 35.61, 42.42, 48.31, 50.20, 65.56, 119.43, 123.40, 125.33, 126.66, 126.99, 127.05, 136.30, 143.27, 149.13, 154.97

(±)-N-Phenylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester; NMR ($CDCl_3$): 20.52, 20.61, 36.91, 39.44, 42.25, 48.22, 62.66, 118.36, 119.46, 123.50, 125.32, 127.11, 127.99, 130.15, 132.63, 139.65, 141.33, 145.16, 152.21, 156.00

(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenoxycarbonylamino]acetic acid ethyl ester hydrochloride
Tlc: R_f 0.14 (4); m.p. colourless crystals (from acetone, 21% yield); NMR ($CDCl_3$): 16.76, 16.86, 18.45, 20.96, 31.37, 42.20, 46.13, 54.56, 65.50, 123.10, 126.98, 127.66, 128.72,

130.14, 134.05, 134.72, 135.22, 141.37, 148.47, 165.12, 170.71

(±)-N-Ethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N-ethylcarbamoyloxybenzyl ester, tlc: R_f 0.36 (3); NMR ($CDCl_3$): 15.00, 19.23, 19.40, 33.26, 36.00, 39.62, 42.35, 48.12, 65.95, 118.30, 125.45, 127.08, 128.33, 130.37, 134.24, 144.44, 155.44, 157.74

(±)-N,N-Dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester
NMR ($CDCl_3$): 20.59, 20.66, 30.59, 35.96, 36.40, 36.74, 36.98, 42.03, 48.26, 50.09, 67.09, 119.04, 123.23, 123.49, 125.01, 126.67, 127.72, 129.33, 133.65, 143.43, 150.99, 155.63.

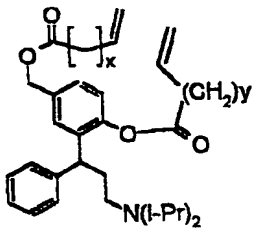
(±)-N,N-Diethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N,N-diethylcarbamoyloxybenzyl ester
NMR ($CDCl_3$): 13.31, 13.64, 13.89, 20.33, 20.71, 31.57, 37.97, 41.55, 42.37, 48.46, 51.00, 67.23, 120.00, 123.39, 124.82, 126.31, 126.95, 127.33, 150.36, 157.18, 158.97.

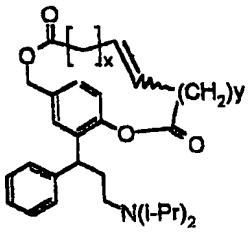
(±)-{4-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxy-methyl-phenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester (formula VII', X = Y = NH, n = 4) tlc: R_f 0.60 (6); dihydrochloride m.p. 142.5-145.6°C

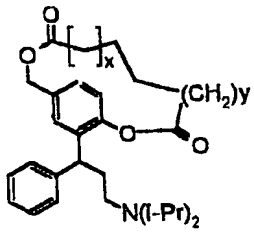
(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester, R_f 0.67 (4)

(±)-Carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester, R_f 0.87 (4)

g) **Intramolecular cyclic diesters via Ring Closing Metathesis (RCM)**







Example:

(±)-Pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester (x = y = 2)

A cooled (4°C) mixture of pent-4-enoic acid, isobutyl chloroformate, and triethylamine (each 5.84 mmol) in 10 ml of dichloromethane was stirred 5 hrs under an atmosphere of dry nitrogen gas. The cooling bath was then removed and both triethylamine (1.46 mmol) and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (1.46 mmol) were added in one portion. After 18 hrs the mixture was diluted with dichloromethane (30 ml), washed several times with water and finally aqueous 5% sodium hydrogen carbonate solution. After drying (sodium sulphate), filtration and evaporation the oily residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave *(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxy-*

methyl)-phenyl ester as a pale yellow syrupy oil (50% yield), tlc: (4) 0.75. NMR ($CDCl_3$): 18.95, 20.77, 27.75, 28.87, 33.58, 36.83, 42.13, 43.72, 48.71, 65.85, 70.55, 115.47, 115.99, 122.45, 126.26, 127.08, 127.96, 128.11, 128.83, 133.73, 136.38, 136.79, 137.04, 143.77, 148.46, 171.11, 172.78.

Intramolecular cyclic diesters of 1,ω-dioic acids and Intermediate B

Example

Intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol

Grubbs catalyst (benzylidene-bis-(tricyclohexylphosphine)-dichlororuthenium, 16 mg, 0.002 mmol, 2 mol-%) was added to a solution of *(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester* (483 mg, 0.96 mmol) in dichloromethane (150 ml) and the mixture was refluxed for 96 hrs. under an atmosphere of nitrogen gas, after which all of the starting material was consumed as indicated by tlc. The mixture was filtered through a short pad of basic alumina, and the solvent was removed in vacuum. Flash chromatography (solvent system (4)) afforded the intermediate intramolecular cyclic diester of oct-4-ene-1,8-dioic acid and 2-(3-diisopropylamino)-1-(phenylpropyl)-4-hydroxymethyl-phenol (324 mg) as a colourless syrup (tlc: (4) R_f 0.68) in 71% yield, mixture of two geometrical isomers. NMR ($CDCl_3$, major isomer): 19.24, 20.61, 23.11, 25.62, 30.55, 33.53, 35.02, 42.41, 48.29, 50.20, 65.30, 114.46, 124.33, 125.58, 127.15, 128.70, 129.29, 131.10, 132.46, 139.54, 146.76, 147.98, 173.76, 174.39.

A portion of this material (140 mg) was dissolved in ethyl acetate (10 ml) and hydrogenated at room temperature in the

presence of palladium-on carbon catalyst to afford the *intramolecular cyclic diester of octane-1,8-dioic acid and 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenol* in essentially quantitative yield, 139 mg, colourless oil, tlc: (4) 0.71.

NMR ($CDCl_3$): 19.36, 20.73, 24.84, 25.28, 28.90, 29.70, 30.57, 33.72, 34.37, 42.39, 48.26, 50.20, 65.26, 114.45, 124.37, 127.11, 128.67, 129.29, 131.18, 132.45, 139.52, 146.77, 147.69, 173.90, 174.15.

Poly-co-DL-Lactides of Intermediate B

All reagents were dried over P_2O_5 in vacuum (< 1 mbar) and at room temperature. The reactions were carried out at room temperature in an atmosphere of dry, oxygen-free nitrogen.

Low Molecular Weight Copolymer

A 15% solution of n-butyllithium (0.36 ml) was injected through a rubber septum into a stirred solution of 2-(3-diisopropylamino-phenylpropyl)-4-hydroxymethyl-phenol (100 mg, Intermediate B) and DL-dilactide (1.5 g) in 15 ml of dry toluene. The polymerization was allowed to proceed for 4 days at room temperature. Distilled water (10 ml) was then added in order to terminate the polymerization. The organic phase was separated and slowly dropped into 200 ml of methanol. The precipitated colourless oil was treated with water (100 ml) and then dried in high vacuum for 48 hrs.

The copolymer was obtained in 72.7% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 2000-4000 and a weight content of Intermediate B of about 8.4% (NMR). Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) analysis showed a Mw of 1108 and a Mn of 702.

High Molecular Weight Copolymer

The high molecular weight copolymer was prepared as described above with the exception that 3.0 g of DL-dilactide was used. Precipitation by methanol gave a fluffy white solid which was carefully washed with water and then dried as desribed to give the copolymer in 81% yield. NMR analysis (see below) indicated an average molecular weight range of M_n 4000-8000 and a weight content of Intermediate B of about 2.0%. Tlc analysis showed the absence of monomeric Intermediate B. Gel permeation chromatography (GPC) showed a Mw of 9347 and a Mn of 6981. Differential scanning calorimetry (DSC) provided a Tg of 42.5°C.

NMR Analysis

The ^1H NMR resonance signals of the poly-lactyl chain were clearly separated from the copolymeric part of Intermediate B (solvent $CDCl_3$):

CH_3 resonances of the poly-lactyl chain: 1.30-1.60 ppm

CH resonances of the poly-lactyl chain: 5.10-5.30 ppm

CH resonances of the connecting lactyl units with the two hydroxy groups of Intermediate B: 4.8-5.0 ppm and 5.5-5.7 ppm.

Polymer bound Intermediate B: 1.06-1.11 (CH_3), 2.20-2.30 ($CH_2\underline{CH_2}$), 2.40-2.80 ($N\underline{CH_2}$), 3.30-3.50 ($N\underline{CH}$), 4.45-4.55 ($\underline{CH}CH_2$), 4.70-4.80 ($\underline{CH_2}$-OCO-lactyl), 6.70-7.30 (aryl $\underline{CH}$).

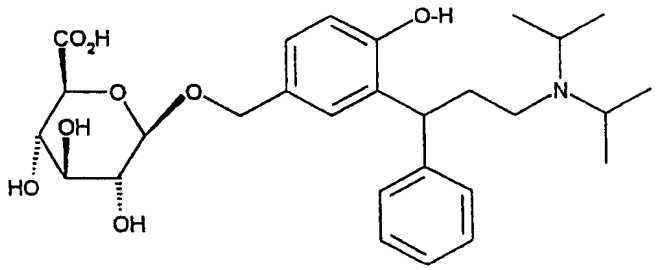
h) Inorganic ester

Example:

(±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester
Hydrochloride

To a stirred solution of chlorosulphonic acid (116 mg, 1.0 mmol) in 5 ml of dry diethyl ether was slowly added at 0°C a solution of (±)-benzoic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester (445.6 mg, 1.0 mmol) in 3 ml of dry diethyl ether. The gel formed immediately during the addition was stirred at room temperature until it became a crystalline consistency (ca. 1 hr). The precipitate was washed several times with diethyl ether and then dried in vacuum to give 0.52 g (46% yield) colourless crystals, m.p. 63-65°C. NMR ($CDCl_3$): 16.85, 17.03, 18.32, 18.49, 32.01, 42.29, 46.23, 55.23, 55.50, 69.24, 122.52, 126.94, 127.15, 129.04, 129.76, 130.25, 133.89, 134.93, 136.85, 141.87, 147.80, 165.19.

i) Benzylic 1-O-β-D-glucuronide of 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol
((±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol)



A solution of methyl 2,3,4-triacetyl-1-α-D-glucuronosyl-bromide (2.07 g, 4.64 mmol) in 24 ml of dry toluene was cooled to -25°C under an atmosphere of nitrogen and then treated with a solution of (±)-benzoic acid 2-(3-diisopropyl-amino-1-phenylpropyl)-4-hydroxymethylphenyl ester in 7 ml of toluene. To this mixture was added dropwise with stirring and under protection from light a solution of silver triflate in 14 ml of toluene (immediate formation of a white precipitate). The cooling bath was removed after 15 min and pyridine (0.38 ml) was added. The mixture was diluted with ethyl acetate (200 ml), filtered and the clear yellow filtrate was washed sequentially with aqueous solutions of sodium thiosulphate (5%), sodium hydrogen carbonate (5%), and sodium chloride (20%). The solution was dried with solid sodium sulphate, treated with charcoal, filtered and evaporated to dryness. The waxy residue was re-dissolved in a small volume of a solvent mixture consisting of ethyl acetate/heptane/triethylamine (65/30/5, vol.-%) and applied on a silica gel flash chromatography column. Elution of the column with the same solvent mixture, collection of the appropriate fractions, and evaporation of the combined fractions gave *(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(2,3,4-triacetyl-1β-D-glucuronosyloxymethyl)-phenyl ester*, colourless syrup, tlc (4) 0.70 (starting amine: 0.31, bromo glycoside: 0.23), yield 14%.

NMR ($CDCl_3$, mixture of diastereomers): 20.41, 20.50, 20.60, 20.65, 20.84, 36.49, 42.44, 43.65, 48.73, 52.91, 69.46, 70.43, 71.12, 72.11, 72.60, 73.99, 99.19, 122.91, 126.23, 126.38, 126.54, 127.60, 127.92, 128.06, 128.09, 128.31, 128.59, 129.38, 130.22, 133.67, 134.31, 137.41, 143.52, 148.46, 164.82, 167.26, 169.21, 169.39, 170.07.

A portion (350 mg) of the above described material was dissolved and hydrolyzed in a solvent mixture consisting of tetrahydrofuran/methanol/aqueous potassium hydroxide (excess, 12 hrs, 22°C). The mixture was evaporated, re-dissolved in 5 ml of water and the pH was adjusted to 8.3. This solution was applied to a chromatography column charged with prewashed XAD 2 resin (50 g). The column was washed with water (ca. 250 ml) and then eluted with methanol. Collection of the appropriate methanol fractions, and evaporation of the combined fractions in vacuum gave 111 mg of

(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucurono-syloxymethyl)-phenol, sodium salt,

amorphous colourless solid, m.p. ≅ 110-124°C (dec.), tlc (4) 0.12. NMR (CD_3OD, major isomer): 19.43, 19.67, 33.26, 39.63, 42.27, 48.23, 69.76, 73.55, 74.70, 75.95, 78.03, 107.64, 117.95, 125.51, 127.36, 128.33, 133.83, 134.77, 144.49, 155.36, 176.76.

II. Incubations of different compounds of the invention with human liver S 9-fraction

a) Incubation of unlabelled substrates

A pooled human liver S 9-preparation was used to show the in-vitro metabolism of different compounds of the invention and to prove the generation of the active metabolite by enzymatic process.

The pooled human liver S 9-preparation was delivered by Gentest, Woburn, MA, USA.

In a routine assay, 25 µL of pooled human liver S9 (20 mg protein/mL, H961, Gentest, Woburn, MA, USA) was incubated

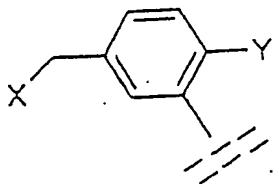
for 2 hrs at 37°C with 40 µM substrate in a 0.01 M potassium phosphate buffer in the presence of NADPH (1 mM). The reaction was quenched by the addition of concentrated perchloric acid and precipitating protein was removed by centrifugation. The supernatant was adjusted to pH 3 with concentrated potassium phosphate solution, centrifuged, and injected into the HPLC for analysis of the respective products.

The analysis of the non-deuterated compounds was performed by a routine High Pressure Liquid Chromatography (HPLC) method with UV-detection.

The incubation results expressed in (%) of theoretical turnover are presented in Fig. 1.

They ranged from 96 to 63.2%. The formation of the active metabolite is dependent on the substituents both at the benzylic and phenolic side of the respective compounds.

Explanation:
The prodrugs introduced in the assay show the following chemical structure:



chemical structure	X-/-Y	
AcO-/-OAc	means	acetate
HO-/-OBut	means	hydroxy and n-butyrate
HO-/-OiBut	means	hydroxy and iso-butyrate

iButO-/-OiBut	means	iso-butyrate
ButO-/-OBut	means	n-butyrate
PropO-/-OProp	means	proprionate
HO-/-OProp	means	hydroxy and proprionate
HO-/-OAc	means	hydroxy and acetate
BzO-/-OBz	means	benzoate and benzoate
AcO-/-OiBut	means	acetate and isobutyrate
AcO-/-OBz	means	acetate and benzoate

b) Incubation of labelled substrates

The metabolic degradation of the unlabelled hydroxy metabolite (i.e. Intermediate B) and the deuteriated hydroxy-metabolite (Intermediate d_2B) were compared in vitro. Used were the respective enantiomers and the racemates.

The hydroxy metabolite and the deuteriated hydroxy-metabolite expressed significant differences in the rate to produce the corresponding carboxylic acid.

The measurement was performed with an incubation time of 3 hrs at 37.0°C in a concentration of 40 µM. The formation of the carboxylic acid from the deuteriated hydroxy-metabolite showed a significantly decreased velocity of 10%.

These in-vitro experiments indicate a reduced metabolic turnover of the deuteriated compound in vitro, which may result in higher plasma levels.

c) Receptor binding study

WO 94/11337 discloses that the active metabolite has high affinity to muscarinic receptors in the guinea-pig bladder. Different compounds of the present invention were tested in

a well established standardized assay, measuring the binding of [^{3}H]-methylscopolamine to recombinant human M3 receptors. BSR-M3H cells transfected with a plasmid encoding the human muscarinic M3 receptor were used to prepare membranes in modified Tris-HCl pH 7.4 buffer using standard techniques. An aliquot of the membrane preparation was incubated with [^{3}H]-methylscopolamine in the presence or absence of different concentrations of several compounds of the invention for 60 minutes at 25°C. Nonspecific binding was estimated in the presence of 1 μM atropine. Membranes were filtered and washed three times and the filters were counted to determine the amount of [^{3}H]-methylscopolamine specifically bound. The following table shows the IC_{50} values of several compounds of the invention in the M3 receptor binding assay.

Interaction with human M3 receptors in vitro

Prodrug	IC_{50} [nM]
(+)HO-/-OH	8.7
(-)HO-/-OH	1300
(+)HO-/-OiBut	159
(+)HO-/-OBz	172
BzO-/-OBz	2400
AcO-/-OiBut	3600
AcO-/-OBz	5400

These data clearly showed that derivatization at the phenolic hydroxyl moiety results in an about 20 times less potent binding. If both functionalities are derivatized, the binding is even more dramatically reduced. Furthermore, it is demonstrated that the enantiomers of the active metabolite exhibit a marked difference in the binding characteristics to human M3 receptors.

The compounds were tested for their anticholinergic activity in a standard tissue assay, the guinea-pig ileum. A segment of ileum was obtained from Duncan Hartley guinea-pigs which were sacrified by cervical dislocation. The tissue was placed under 1 g tension in a 10 ml bath containing Krebs' solution (pH 7.4, 32°C) and the concentration-dependent ability of different compounds to reduce the methacholine-induced (0.6 μM) contractile response was recorded. The IC_{50} values for the different substances were calculated and examples are presented in the following table.

Anticholinergic activity in guinea-pig ileum in vitro

Prodrug	IC_{50} [nM]
(+)HO-/-OH	20
(-)HO-/-OH	680
(+)HO-/-OiBut	57
(+)HO-/-OBz	180
(+)BzO-/-OBz	220
(+)AcO-/-OiBut	240

These data confirm the results obtained in the receptor binding assays and demonstrate that the anticholinergic activity of the compounds decreases with increased derivatization.

d) Biological membranes

Different compounds of the invention were tested for their ability to penetrate the human skin (200 μm thick) in the "Flow through cell" at 32°C according to Tiemessen et al. (Acta Pharm. Technol. 1998; 34:99-101). Phosphate buffer (pH 6.2) was used as the acceptor medium. Samples were drawn at different time points and analysed by RP-HPLC with UV de-

tection (220 nm). Permeation profiles were plotted and mean flux rates of different substances were calculated by linear regression analysis. The data obtained for different compounds of the invention are summarized in the following table.

Penetration through human skin

Prodrug	Flux rate [$\mu g/cm^2/24hrs$]
HO-/-OH	3
HO-/-OiBut	150
iButO-/-OiBut	60
PropO-/-OProp	70

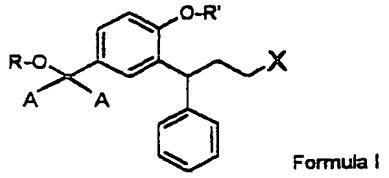
Disubstitution of the hydroxy group of HO-/-OH leads to a ≥ 20-fold increase in skin permeation in relation to the parent HO-/-OH. Suprisingly monosubstitution of the penolic hydroxy group resulted in even higher 50-fold penetration rate through human skin.

Taken together, these biological data clearly demonstrate that the compounds of the invention have a reduced affinity to bind to human muscarinic M3 receptors. They exhibit an increased penetration through biological membranes, e.g. the human skin, and they are rapidly transformed to the active metabolite, once they have entered the systemic circulation as shown by the in vitro metabolism by the human liver S9 preparation.

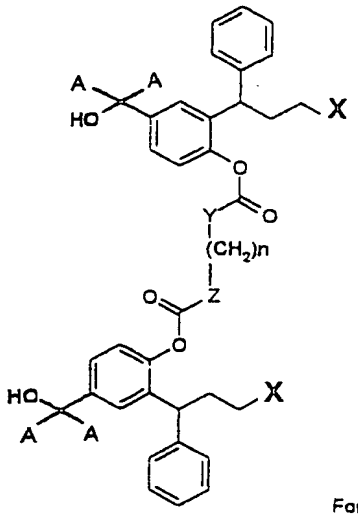
Thus, the antimuscarinic prodrugs according to this invention showed a profile that defines excellent prodrugs.

Claims

1. 3,3-Diphenylpropylamines of the general formulae I and VII':



Formula I



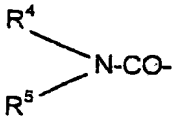
Formula VII'

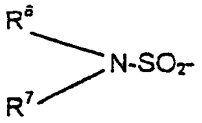
wherein R and R' are independently selected from

a) hydrogen, C_1-C_6 alkyl, C_3-C_{10} cycloalkyl, substituted or unsubstituted benzyl, allyl or carbohydrate; or

b) formyl, C_1-C_6 alkylcarbonyl, cycloalkylcarbonyl, substituted or unsubstituted arylcarbonyl, preferably benzoyl; or

c) C_1-C_6 alkoxycarbonyl, substituted or unsubstituted aryloxycarbonyl, benzoylacyl, benzoylglycyl, a substituted or unsubstituted amino acid residue; or

d)  wherein R^4 and R^5 independently represent hydrogen, C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 4 carbon atoms and wherein R^4 and R^5 may form a ring together with the amine nitrogen; or

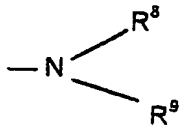
e)  wherein R^6 and R^7 independently represent C_1-C_6 alkyl, substituted or unsubstituted aryl, preferably substituted or unsubstituted phenyl, benzyl or phenoxyalkyl wherein the alkyl residue has 1 to 6 carbon atoms; or

f) an ester moiety of inorganic acids,

g) $-SiR_aR_bR_c$, wherein R_a, R_b, R_c are independently selected from C_1-C_4 alkyl or aryl, preferably phenyl,

with the proviso that R' is not hydrogen, methyl or benzyl if R is hydrogen, R is not ethyl if R' is hydrogen,

X represents a tertiary amino group of formula Ia



Formula Ia

wherein R^8 and R^9 represent non-aromatic hydrocarbyl groups, which may be the same or different and which together contain at least three carbon atoms, and wherein R^8 and R^9 may form a ring together with the amine nitrogen,

Y and Z independently represent a single bond between the $(CH_2)_n$ group and the carbonyl group, O, S or NH,

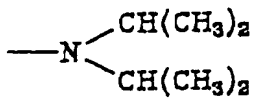
A represents hydrogen (^1H) or deuterium (^2H),

n is 0 to 12

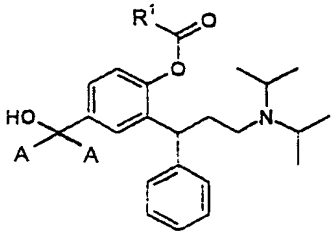
and

their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

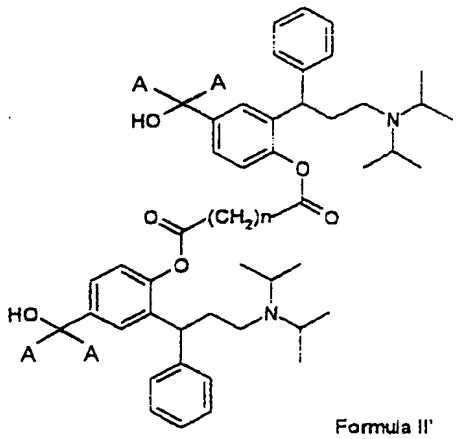
2. 3,3-Diphenylpropylamines as claimed in claim 1, wherein X is



3. 3,3-Diphenylpropylamines as claimed in claim 2 selected from phenolic monoesters represented by the general formulae II and II'



Formula II



Formula II'

wherein R^1 represents hydrogen, C_1-C_6 alkyl or phenyl.

4. 3,3-Diphenylpropylamines as claimed in claim 3 selected from:

(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-n-butyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

R-(+)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

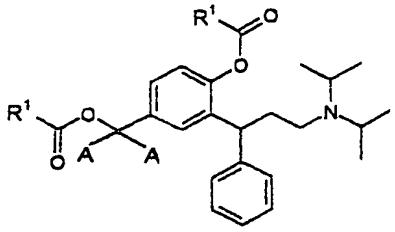
(±)-2,2-dimethylpropionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-2-acetamidoacetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,

(±)-cyclopentanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-cyclohexanecarboxylic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methylbenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-acetoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-1-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-naphthoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-chlorobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-methoxybenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-4-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-2-nitrobenzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-malonic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,
(±)-succinic acid bis-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenyl]ester,

(±)-pentanedioic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester,
(±)-hexanedioic acid bis-[2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethyl-phenyl]ester.

5. 3,3-Diphenylpropylamines as claimed in claim 2 selected from identical diesters represented by the general formula III



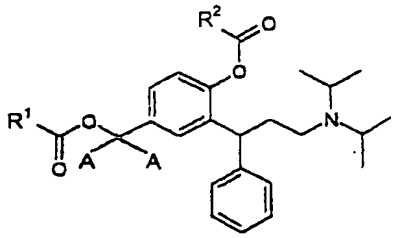
Formula III

wherein R^1 is defined as in claim 3.

6. 3,3-Diphenylpropylamines as claimed in claim 5 selected from:
(±)-formic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-acetic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-propionic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-propionyloxymethylphenyl ester,
(±)-n-butyric acid 4-n-butyryloxymethyl-2-(3-diisopropyl-amino-1-phenylpropyl)-phenyl ester,
(±)-isobutyric acid 2-(3-diisopropylamino-1-phenylpropyl)-4-isobutyryloxymethylphenyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-(2,2-dimethyl-propionyloxy)-benzyl ester,
(±)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,

R-(+)-benzoic acid 4-benzoyloxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-pent-4-enoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-(pent-4-enoyloxymethyl)-phenyl ester,
cyclic oct-4-ene-1,8-dioate of Intermediate B,
cyclic octane-1,8-dioate of Intermediate B,
poly-co-DL-lactides of Intermediate B.

7. 3,3-Diphenylpropylamines as claimed in claim 2 selected from mixed diesters represented by the general formula IV



Formula IV

wherein R^1 is defined as in claim 3

and

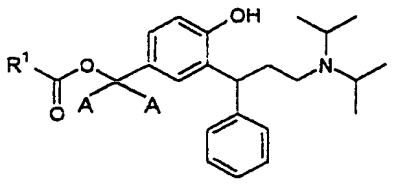
R^2 represents hydrogen, C_1-C_6 alkyl or phenyl

with the proviso that R^1 and R^2 are not identical.

8. 3,3-Diphenylpropylamines as claimed in claim 7 selected from:
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,
(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-formyloxymethylphenyl ester,

(±)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
R-(+)-benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-acetoxymethylphenyl ester,
(±)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
R-(+)-isobutyric acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2,2-dimethylpropionic acid 4-acetoxymethyl-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester.

9. 3,3-Diphenylpropylamines as claimed in claim 2 selected from benzylic monoesters represented by the general formula V



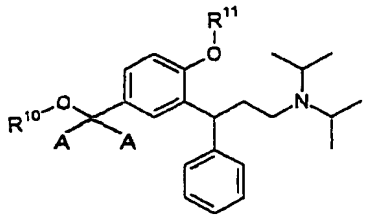
Formula V

wherein R^1 is defined as in claim 3.

10. 3,3-Diphenylpropylamines as claimed in claim 9 selected from:
(±)-formic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-acetic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,

(±)-propionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-butyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-isobutyric acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-2,2-dimethylpropionic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester,
(±)-benzoic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-hydroxybenzyl ester.

11. 3,3-Diphenylpropylamines as claimed in claim 2 selected from ethers and silyl ethers represented by the general formula VI



Formula VI

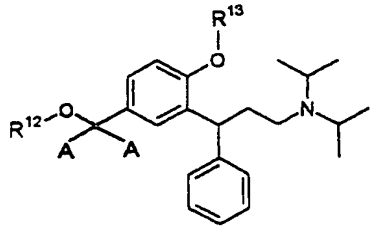
wherein at least one of R^{10} and R^{11} is selected from C_1-C_6 alkyl, benzyl or $-SiR_aR_bR_c$ as defined in claim 1 and the other one of R^{10} and R^{11} may additionally represent hydrogen, C_1-C_6 alkylcarbonyl or benzoyl.

12. 3,3-Diphenylpropylamines as claimed in claim 11 selected from:
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenol,

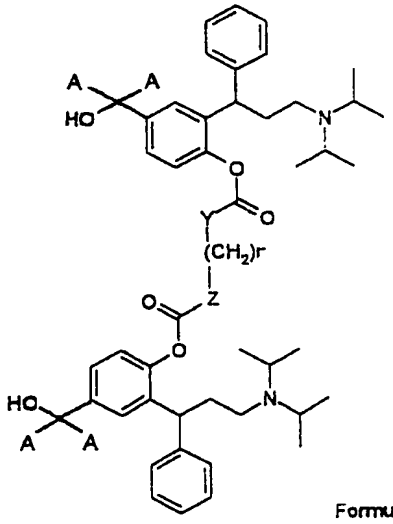
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethyl-phenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-propoxymethyl-phenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-isopropoxy-methylphenol,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-butoxymethyl-phenol,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-methoxymethylphenyl ester,
(±)-acetic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxymethylphenyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-trimethyl-silanyloxymethylphenol,
(±)-diisopropyl-[3-phenyl-3-(2-trimethylsilanyloxy-5-tri-methylsilanyloxymethylphenyl)-propyl]-amine,
(±)-[3-(3-diisopropylamino-1-phenylpropyl)-4-trimethyl-silanyloxyphenyl]-methanol,
(±)-diisopropyl-[3-(5-methoxymethyl-2-trimethylsilanyl-oxyphenyl)-3-phenylpropylamine,
(±)-diisopropyl-[3-(5-ethoxymethyl-2-trimethylsilanyl-oxyphenyl)-3-phenylpropylamine,
(±)-[4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-4-(tert.-butyl-dimethylsilanyloxy)-3-(3-diisopropylamino-1-phenylpropyl)-phenol,
(±)-acetic acid 4-(tert.-butyl-dimethylsilanyloxy)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-{3-[2-(tert.-butyl-dimethylsilanyloxy)-5-(tert.-butyl-dimethylsilanyloxymethyl)-phenyl]-3-phenylpropyl}-diisopropylamine,

(±)-[4-(tert.-butyl-diphenylsilanyloxy)-3-(3-diisopropyl-amino-1-phenylpropyl)-phenyl]-methanol,
(±)-acetic acid 4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diisopropylamino-1-phenylpropyl)-phenyl ester,
(±)-4-(tert.-butyl-diphenylsilanyloxymethyl)-2-(3-diiso-propylamino-1-phenylpropyl)-phenol,
(±)-{3-[2-(tert.-butyl-diphenylsilanyloxy)-5-(tert.-butyl-di-phenylsilanyloxymethyl)-phenyl]-2-phenylpropyl}-diisopropyl-amine,
(±)-acetic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester,
(±)-benzoic acid 4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzyl ester,
(±)-isobutyric acid 4-benzyloxy-3-(3-diisopropylamino-1-phenylpropyl)-benzyl ester,
(±)-2-(3-diisopropylamino-1-phenylpropyl)-4-(1β-D-glucurono-syloxymethyl)-phenol.

13. 3,3-Diphenylpropylamines as claimed in claim 2 selected from carbonates and carbamates represented by the general formulae VII and VIII

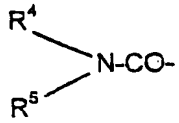


Formula VII



Formula VIII

wherein Y, Z and n are as defined in claim 1 and wherein R^{12} and R^{13} represent a C_1-C_6 alkoxycarbonyl group or



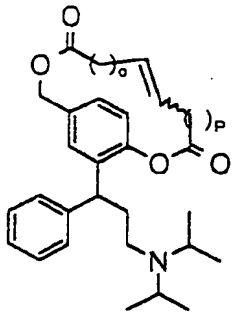
wherein R^4 and R^5 are as defined in claim 1.

14. 3,3-Diphenylpropylamines as claimed in claim 13 selected from:
(±)-N-ethylcarbamic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-N,N-dimethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
(±)-N,N-diethylcarbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester
(±)-N-phenylcarbamic acid 2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl ester,
(±)-[2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenoxycarbonylamino]acetic acid ethyl ester hydrochloride,
(±)-N-ethylcarbamic acid 3-(3-diisopropylamino-1-phenyl-propyl)-4-N-ethylcarbamoyloxybenzyl ester,
(±)-N,N-dimethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-dimethylcarbamoyloxybenzyl ester,
(±)-N,N-diethylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N,N-diethylcarbamoyloxybenzyl ester,
(±)-N-phenylcarbamic acid 3-(3-diisopropylamino-1-phenylpropyl)-4-N-phenylcarbamoyloxybenzyl ester,
(±)-{4-[2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenoxycarbonylamino]-butyl}-carbamic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester ethyl ester,

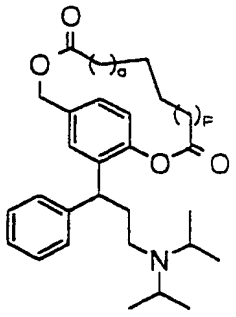
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl ester phenyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-ethoxycarbonyloxymethylphenyl ester ethyl ester,
(±)-carbonic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-phenoxycarbonyloxymethylphenyl ester phenyl ester.

15. 3,3-Diphenylpropylamines selected from

(i) compounds of the formulae IX and IX'



Formula IX



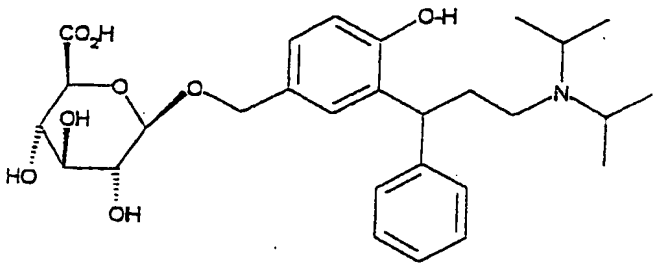
Formula IX'

wherein o and p are the same or different and represent the number of methylene units $-CH_2-$ and may range from 0 to 6,

(ii) (±)-Benzoic acid 2-(3-diisopropylamino-1-phenylpropyl)-4-sulphooxymethyl-phenyl ester

(iii) Poly-co-DL-lactides of 2-(3-diisopropylamino-phenyl-propyl)-4-hydroxymethyl-phenol

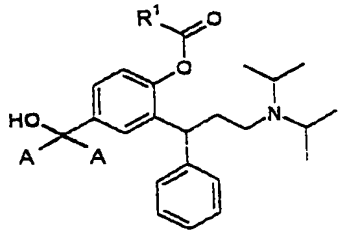
(iv) (±)-2-(3-Diisopropylamino-1-phenylpropyl)-4-(1β-D-glucuronosyloxymethyl)-phenol having the formula



and

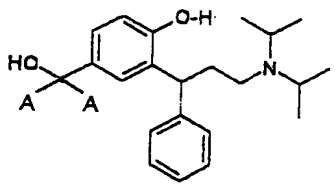
their salts with physiologically acceptable acids, their free bases and, when the compounds can be in the form of optical isomers, the racemic mixture and the individual enantiomers.

16. A process for the production of phenolic monoesters represented by the general formula II

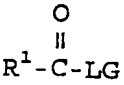


Formula II

as defined in claim 3, which comprises treatment of a compound of the formula

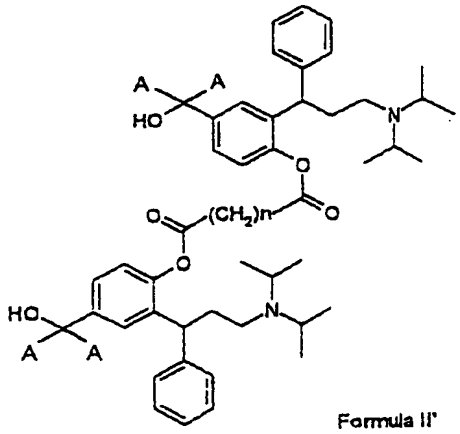


with an equivalent of an acylating agent selected from



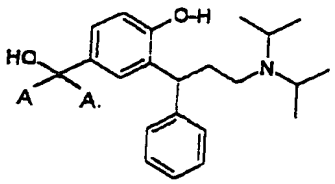
wherein LG represents a leaving group selected from halogenide, carboxylate and imidazolide and R^1 is as defined in claim 3, in an inert solvent in the presence of a condensating agent.

17. A process for the production of phenolic monoesters represented by the general formula II'

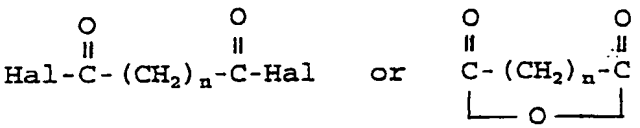


Formula II'

as defined in claim 3, which comprises treatment of two equivalents of a compound of the formula

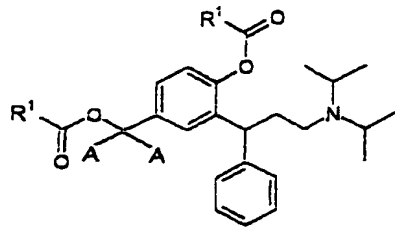


with an acylating agent selected from



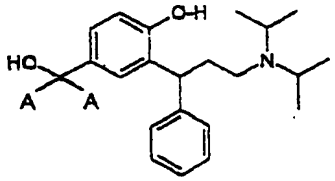
wherein Hal represents a halogen atom.

18. A process for the production of identical diesters represented by the general formula III



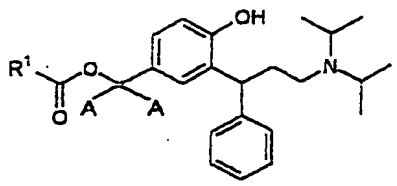
Formula III

as defined in claim 5, which comprises treatment of a compound of the formula



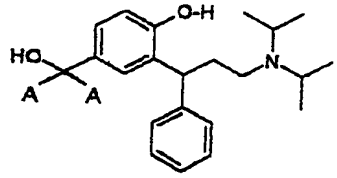
with at least two equivalents of the acylating agent as defined in claim 16.

19. A process for the preparation of benzylic monoesters represented by the general formula V



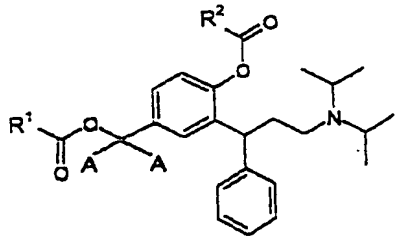
Formula V

as defined in claim 9, which comprises treatment of a compound of the formula



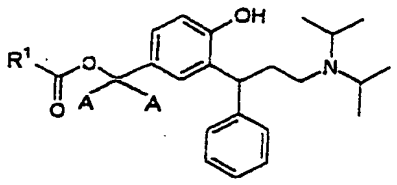
at room temperature and under anhydrous conditions with activated esters in the presence of enzymes selected from lipases or esterases.

20. A process for the preparation of mixed diesters represented by the general formula IV



Formula IV

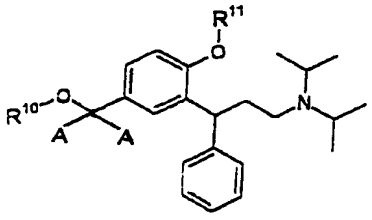
as defined in claim 7, which comprises acylation of a benzylic monoester represented by the general formula V



Formula V

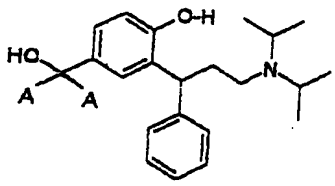
as defined in claim 9 or of a phenolic monoester represented by the formula II as defined in claim 3.

21. A process for the production of ethers represented by the general formula VI



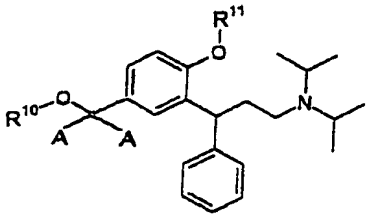
Formula VI

as defined in claim 11 wherein R^{11} is hydrogen which comprises reacting a compound of the formula



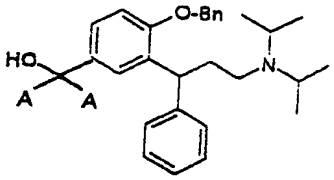
with an alcohol R^{10}-OH in the presence of an esterification catalyst.

22. A process for the preparation of ethers represented by the general formula VI

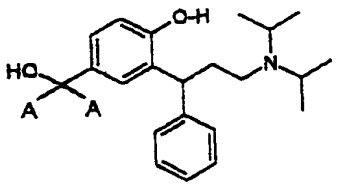


Formula VI

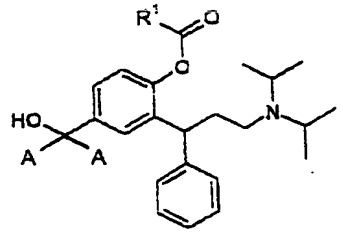
wherein R^{10} and R^{11} are as defined in claim 11, which comprises acid or base treatment of free benzylic alcohols selected from



and

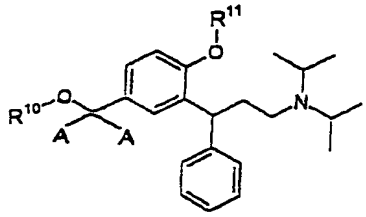


and



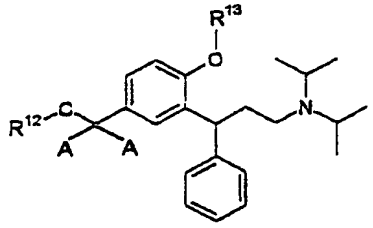
Formula II

or



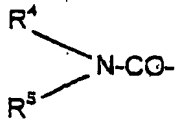
Formula VI

wherein R^{10} is hydrogen or

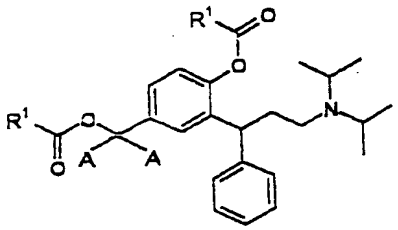


Formula VII

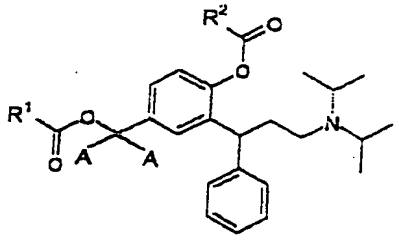
wherein R^{12} is hydrogen and R^{13} represents a C_1-C_6 alkoxycarbonyl group or



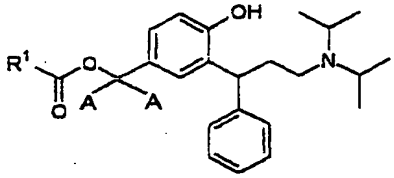
wherein R^4 and R^5 are as defined in claim 1 or of benzylic acylates selected from



Formula III



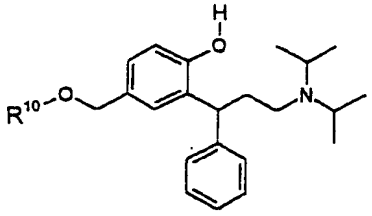
Formula IV



Formula V

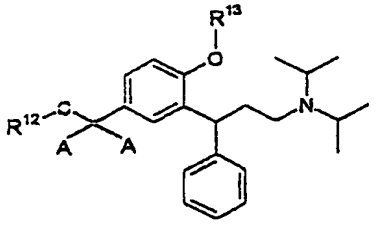
wherein R^1 and R^2 are as defined in claim 7 in the presence of suitable hydroxy reagents.

23. A process for the preparation of ethers of formula VI as defined in claim 11, which comprises treating a compound of the formula

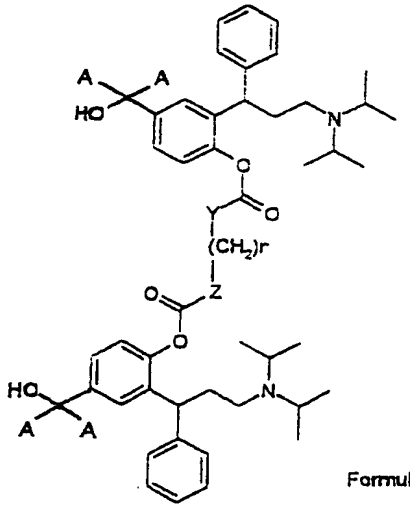


with an alkylating agent selected from alkyl halcgenides, alkyl sulphates and alkyl triflates, said alkyl group having 1 to 6 carbon atoms.

24. A process for the preparation of carbonates and carbamates represented by the general formulae VII and VIII

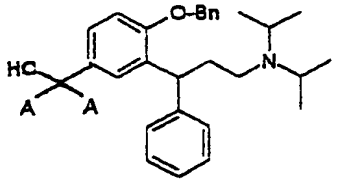


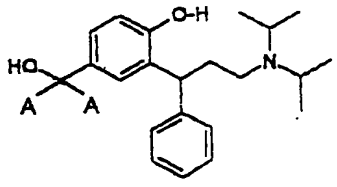
Formula VII

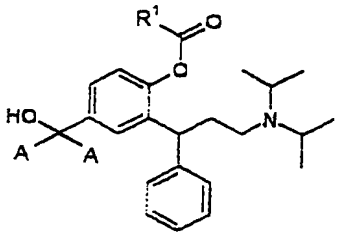


Formula VIII

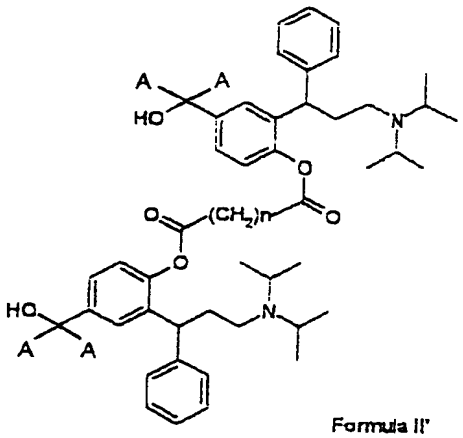
as defined in claim 13, which comprises reacting a compound selected from the group consisting of



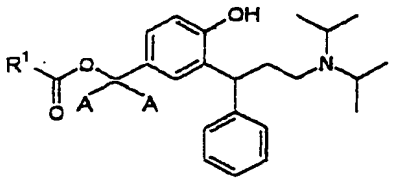




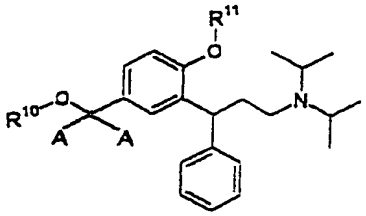
Formula II



Formula II'



Formula V



Formula VI

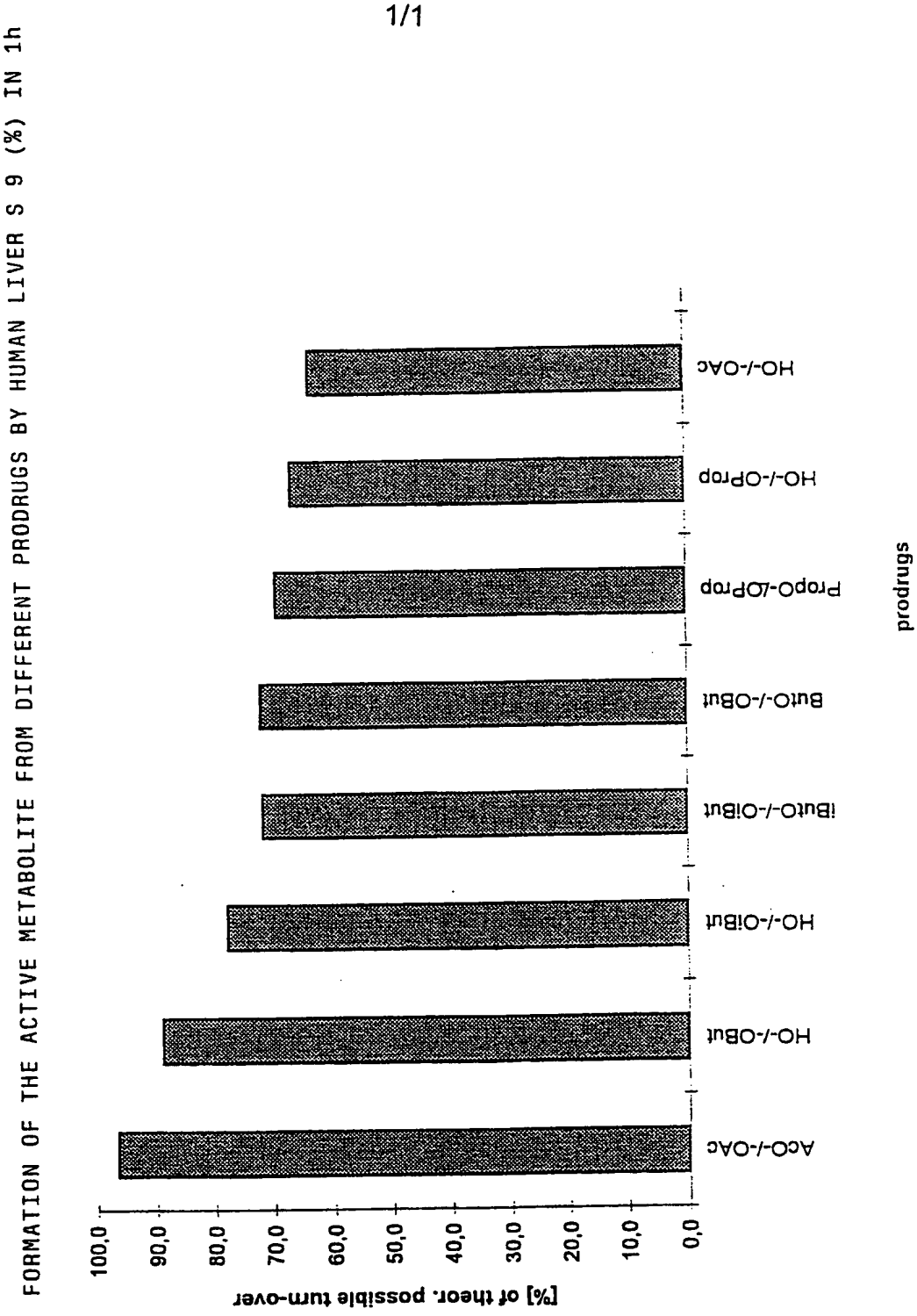
wherein R^1 is defined as in claim 3, n is 0 to 12, Bn is benzyl, one of R^{10} or R^{11} is hydrogen and the other one is as defined in claim 11 with activated carbonyl compounds or carbonyl precursor reagents selected from haloformates, ketenes, activated esters, mixed anhydrides of organic or inorganic acids, isocyanates and isothiocyanates.

25. 3,3-Diphenylpropylamines as claimed in claims 1 to 15 for use as pharmaceutically active substances, especially as antimuscarinic agents.

26. A pharmaceutical composition comprising a 3,3-diphenylpropylamine as claimed in claim 1 to 15 and a compatible pharmaceutical carrier.

27. Use of a 3,3-diphenylpropylamine as claimed in claims 1 to 15 for preparing an antimuscarinic drug.

FIG. 1


FORMATION OF THE ACTIVE METABOLITE FROM DIFFERENT PRODRUGS BY HUMAN LIVER S 9 (%) IN 1h
[%] of theor. possible turn-over
100,0
90,0
80,0
70,0
60,0
50,0
40,0
30,0
20,0
10,0
0,0
AcO-/-OAc
HO-/-OBut
HO-/-OiBut
iButO-/-OiBut
ButO-/-OBut
PropO-/OProp
HO-/-OProp
HO-/-OAc
prodrugs

INTERNATIONAL SEARCH REPORT

Inter. onal Application No
PCT/EP 99/03212

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C1/00 C07C217/62 C07C217/48 C07C219/28 C07C219/22
C07D207/06 C07D295/06 C07C271/08 C07F7/18 C07C307/02
A61K31/135 A61K31/325 A61K31/40 A61K31/435

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 6 C07C C07D C07F A61K

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 94 11337 A (KABI PHARMACIA AB ;JOHANSSON ROLF ARNE (SE); MOSES PINCHAS (SE); N) 26 May 1994 (1994-05-26) cited in the application page 12, line 35 - page 13, line 15 ---	1-3,5,9, 25-27
A	WO 89 06644 A (KABIVITRUM AB) 27 July 1989 (1989-07-27) abstract ---	1-3, 25-27
A	LISBETH NILVEBRANT ET AL.: "Tolterodine - a new bladder-selective antimuscarinic agent" EUROPEAN JOURNAL OF PHARMACOLOGY, vol. 327, 1997, pages 195-207, XP002079629 cited in the application the whole document -----	1,25-27

☐ 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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 July 1999	26/07/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rufet, J

1

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. onal Application No
PCT/EP 99/03212

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9411337 A	26-05-1994	AT 164828 T	15-04-1998
		AU 672458 B	03-10-1996
		AU 5438094 A	08-06-1994
		CA 2148827 A	26-05-1994
		DE 69317898 D	14-05-1998
		DE 69317898 T	15-10-1998
		EP 0667852 A	23-08-1995
		ES 2117155 T	01-08-1998
		FI 952179 A	05-05-1995
		HK 1006349 A	19-02-1999
		HU 72742 A	28-05-1996
		JP 8503208 T	09-04-1996
		NO 951775 A	05-05-1995
		US 5559269 A	24-09-1996
		US 5686464 A	11-11-1997
WO 8906644 A	27-07-1989	AT 65990 T	15-08-1991
		AU 635493 B	25-03-1993
		AU 2932989 A	11-08-1989
		CA 1340223 A	15-12-1998
		DK 172590 A	19-07-1990
		EP 0325571 A	26-07-1989
		EP 0354234 A	14-02-1990
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		HK 64494 A	15-07-1994
		HU 212729 B	28-10-1996
		HU 9400053 A	30-01-1995
		JP 2664503 B	15-10-1997
		JP 3503163 T	18-07-1991
		LU 90259 A	16-09-1998
		NO 173496 C	22-12-1993
		US 5382600 A	17-01-1995

TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT (Under 37 CFR 1.97(b) or 1.97(c))	Docket No. 41946/32854

In Re Application:
Meese, Claus

Serial No.	Filing Date	Examiner	Group Art Unit
10/130214	5/14/2002	~~Not Assigned~~ TUCKER, Z.	~~1614~~ 1624

Payment of Fee

(Only complete if Applicant elects to pay the fee set forth in 37 CFR 1.17(p))

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Dated: August 14, 2002

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TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application Number	10/130214
Filing Date	5/14/2002
First Named Inventor	Meese, Claus
Group Art Unit	~~1614~~ 1624
Examiner Name	~~Not Assigned~~ TUCKER, Z.
Total Number of Pages in This Submission: 1	Attorney Docket No. 41946/32854

ENCLOSURES *(check all that apply)*

- ☐ Charge Deposit Account –20-0823
- ☒ Fee Attached
- ☐ Amendment / Reply
- ☐ Affidavits/declarations(s)
- ☐ Extension of Time Request
- ☐ Express Abandonment Request
- ☒ Information Disclosure Statement
- ☐ Certified Copy of Priority Document(s)
- ☐ Response to Missing Parts - Incomplete Application
- ☐ Response to Missing Parts under 37 CFR 1.52 or 1.53
- ☐ Petition For Revival of an Application for Patent Abandoned Unintentionally Under 37 CFR 1.137(b))
- ☐ Assignment Papers *(for an Application)*
- ☐ Drawing(s)
- ☐ Licensing-related Papers
- ☐ Petition
- ☐ Petition to Convert to a Provisional Application
- ☐ Power of Attorney, Revocation Change of Correspondence Address
- ☐ Terminal Disclaimer
- ☐ Request for Refund
- ☐ CD, Number of CD(s) _____
- ☐ After Allowance Communication to Group
- ☐ Appeal Communication to Board of Appeals and Interferences
- ☐ Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- ☐ Proprietary Information
- ☐ Status Letter
- ☐ Request To Rescind Previous Nonpublication Request
- ☐ Response to Notice of Allowability
- ☐ Other Enclosure(s) *(please identify below)*:

Remarks:

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Firm *or* Individual Name	Paul A. Lesko
Signature	
Date	August 14, 2002

CERTIFICATE OF EXPRESS MAILING

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I hereby certify that this correspondence is being deposited on August 14, 2002 with the United States Postal Service as Express Mail under 37 C.F.R. 1.10 and addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

date: August 14, 2002

Typed or printed name	Paul A. Lesko		
Signature		Date	August 14, 2002

Express Mail No.:EL474165379US

TRANSMITTAL OF INFORMATION DISCLOSURE STATEMENT (Under 37 CFR 1.97(b) or 1.97(c))			Docket No. 41946/32854
In Re Application Of: Meese, Clause			
Serial No.	Filing Date	Examiner	Group Art Unit
10/130214	5/14/2002	~~Not Assigned~~ TUCKER, Z.	~~1614~~ 1624

Title:

STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES

Address to:
Assistant Commissioner for Patents
Washington, D.C. 20231

37 CFR 1.97(b)

1. ☒ The Information Disclosure Statement submitted herewith is being filed within three months of the filing of a national application other than a continued prosecution application under 37 CFR 1.53(d); within three months of the date of entry of the national stage as set forth in 37 CFR 1.491 in an international application; before the mailing of a first Office Action on the merits, or before the mailing of a first Office Action after the filing of a request for continued examination under 37 CFR 1.114.

37 CFR 1.97(c)

2. ☐ The Information Disclosure Statement submitted herewith is being filed after the period specified in 37 CFR 1.97(b), provided that the Information Disclosure Statement is filed before the mailing date of a Final Action under 37 CFR 1.113, a Notice of Allowance under 37 CFR 1.311, or an Action that otherwise closes prosecution in the application, and is accompanied by one of:

   ☐ the statement specified in 37 CFR 1.97(e);

   OR

   ☐ the fee set forth in 37 CFR 1.17(p).

FORM PTO-1390 (REV. 11-2000) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: **41946/32854**

U.S. APPLICATION NO. (If known, see 37 CFR 1.5): New **10/130214**

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/11309	**15 NOVEMBER 2000**	**16 NOVEMBER 1999**

TITLE OF INVENTION
STABLE SALTS OF NOVEL DERIVATIVES OF 3,3,-DIPHENYLPROPYLAMINES

APPLICANT(S) FOR DO/EO/US
MEESE, Claus

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is attached hereto (required only if not communicated by the International Bureau).
   b. ☒ has been communicated by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371(c)(2)).
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154 (d)(4).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
14. ☐ A SECOND or SUBSEQUENT preliminary amendment.
15. ☐ A substitute specification.
16. ☒ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule 13ter.2 and 35 U.S.C. 1.821 – 1.825.
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application under 35 U.S.C. 154(d)(4).
20. ☒ Other items or information: Certificate of Express Mailing;
    Postcard
    Statement Under 37 CFR 3.73(b)

U.S. APPLICATION NO. (if known, see 37 CFR 1.5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
New 10/130294	PCT/EP00/11309	41946/32854

21. ☒ The following fees are submitted:

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) – (5)):

Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and International Search Report not prepared by the EPO or JPO **$1000.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO **$860.00**

International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$710.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$690.00**

International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4) **$100.00**

	CALCULATIONS PTO USE ONLY	
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Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	30- 20 =	10	x $18.00	$	180.00
Independent claims	10- 3 =	7	x $80.00	$	560.00
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ $270.00	$	270.00
			TOTAL OF ABOVE CALCULATIONS =	$	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by 1/2.			+	$	
			SUBTOTAL =	$	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				$	
			TOTAL NATIONAL FEE =	$	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property			+	$	40.00
			TOTAL FEES ENCLOSED =	$	1910.00
				Amount to be refunded:	$
				charged:	$

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c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 20-0823. A duplicate copy of this sheet is enclosed.

d. ☐ Fees are to be charged to a credit card. **WARNING:** Information on this form may become public. **Credit card information should not be included on this form.** Provide credit card information and authorization on PTO-2038.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to review (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Paul A. Lesko, Esq.
Thompson Coburn LLP
One U.S. Bank Plaza
St. Louis, MO 63101
Telephone No.: 314.552.6443
Facsimile No.: 314.552.7000

Signature

Paul A. Lesko
Name

45,364
Registration Number

#4/a

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: MEESE, Claus et al.	**Examiner:** To be assigned
Application No.: To be assigned	**Group Art Unit:** To be assigned
Filed: Herewith	
Title: STABLE SALTS OF NOVEL DERIVATIVES OF 3,3-DIPHENYLPROPYLAMINES	**Docket No.:** 41946/32854

Commissioner for Patents
Box PCT
Washington, DC 20231

PRELIMINARY AMENDMENT

Sir:

Prior to calculation of the filing fee and examination on the merits, kindly amend the above-identified patent application per the following instructions.

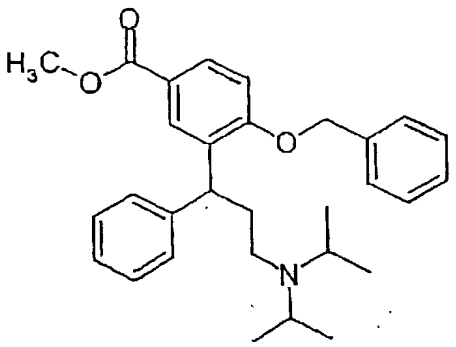
Kindly amend the specification at page one after the title and before the first line of text, by inserting at that point the following sentence -- This patent application claims the benefit of priority under 35 U.S.C. § 119 of German Patent Application No. 199 55 190.1, filed November 16, 1999. German Patent Application No. 199 55 190.1 is incorporated herein in its entirety by reference.--

The amendments to claims 18-21, 23-25, 27, and 28 are pursuant to an Article 34 amendment made to the PCT application on October 5, 2001.

IN THE CLAIMS

At page 56, amend claims 18-21, 23-25, 27, and 28 as follows:

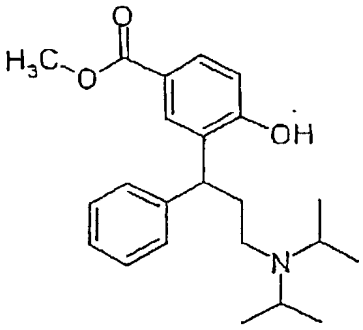
18. (once amended) Compound of formula III



Formula III

in highly pure, crystalline and stable form.

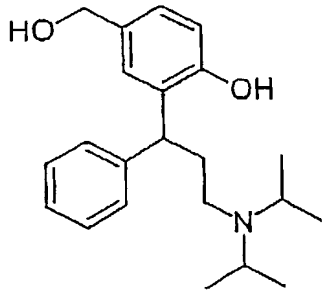
19. (once amended) Compound of formula V



Formula V

in highly pure, crystalline and stable form.

20. (once amended) Compound of formula VI

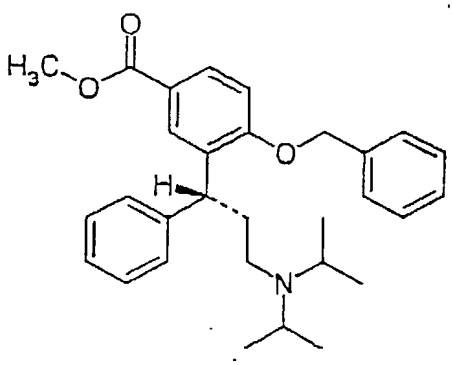


Formula VI

in highly pure, crystalline and stable form.

21. (once amended) Use of a compound in accordance with claims 18 to 20 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds of formula 1 in accordance with claim 1.

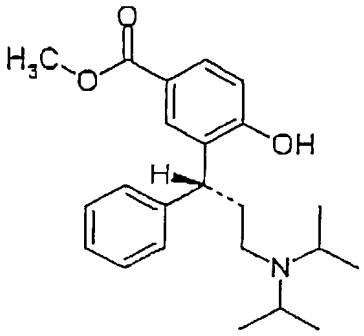
23. (once amended) Compound of formula 3



Formula 3

in highly pure, crystalline and stable form.

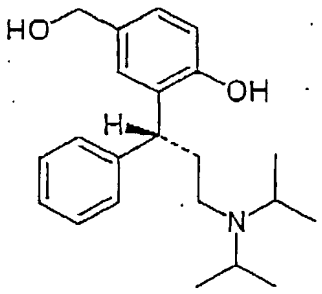
24. (once amended) Compound of formula 5



Formula 5

in highly pure, crystalline and stable form.

25. (once amended) Compound of formula 6

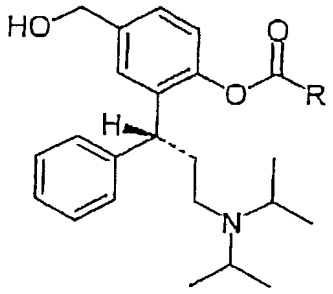


Formula 6

in highly pure, crystalline and stable form.

27. (once amended) Use of a compound in accordance with claims 23 to 26 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds of formula 2 in accordance with claim 3.

28. (once amended) Use of a compound in accordance with claims 23 to 26 as an intermediate product in the manufacture of phenolic monoesters of general formula 1



Formula 1

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl or unsubstituted or substituted phenyl.

Kindly consider this preliminary amendment and enter it into the record of this application. Attached is a clean copy of the claims. All correspondence should to be directed to Paul A. Lesko, Thompson Coburn LLP, One U.S. Bank Plaza, St. Louis, MO 63101, Telephone No.: 314.552.6443, Facsimile No.: 314.552.7000.

Respectfully submitted,

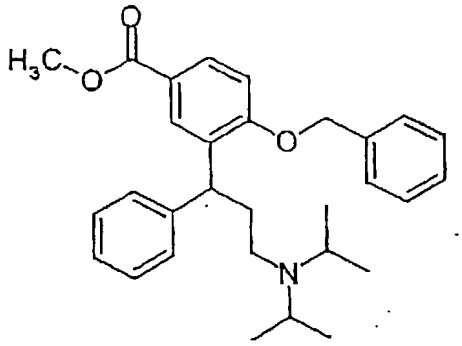
Paul A. Lesko
Registration No. 45,364
Thompson Coburn LLP
One U.S. Bank Plaza
St. Louis, MO 63101
Telephone: 314.552.6443
Facsimile: 314.552.7000

CLEAN COPY OF PARAGRAPH TO BE INSERTED INTO SPECIFICATION

-- This patent application claims the benefit of priority under 35 U.S.C. § 119 of German Patent Application No. 199 55 190.1, filed November 16, 1999. German Patent Application No. 199 55 190.1 is incorporated herein in its entirety by reference.--

Claims

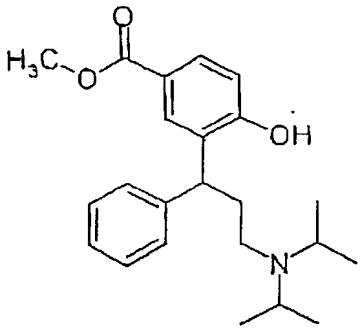
18. Compound of formula III



Formula III

in highly pure, crystalline and stable form.

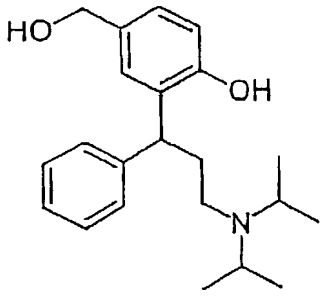
19. Compound of formula V



Formula V

in highly pure, crystalline and stable form.

20. Compound of formula VI

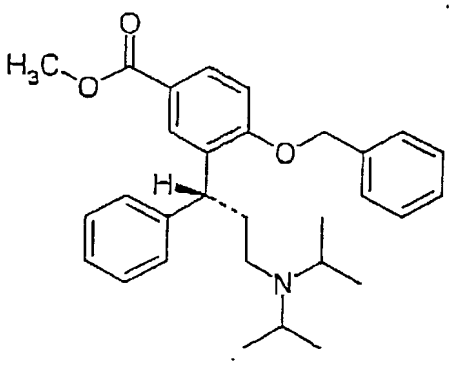


Formula VI

in highly pure, crystalline and stable form.

21. Use of a compound in accordance with claims 18 to 20 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds of formula 1 in accordance with claim 1.

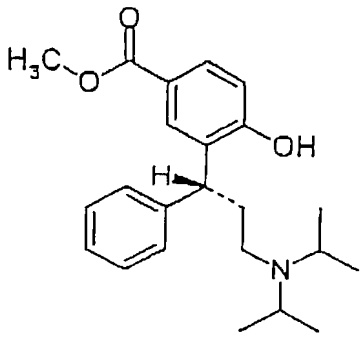
23. Compound of formula 3



Formula 3

in highly pure, crystalline and stable form.

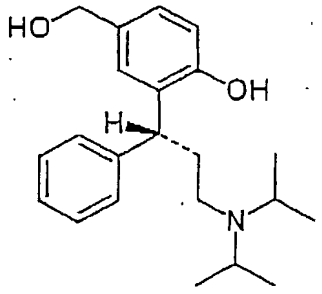
24. Compound of formula 5



Formula 5

in highly pure, crystalline and stable form.

25. Compound of formula 6

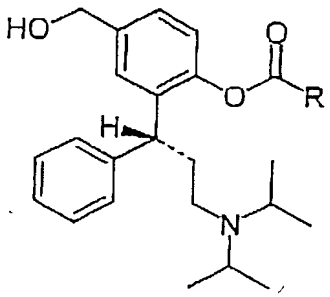


Formula 6

in highly pure, crystalline and stable form.

27. Use of a compound in accordance with claims 23 to 26 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds of formula 2 in accordance with claim 3.

28. Use of a compound in accordance with claims 23 to 26 as an intermediate product in the manufacture of phenolic monoesters of general formula 1



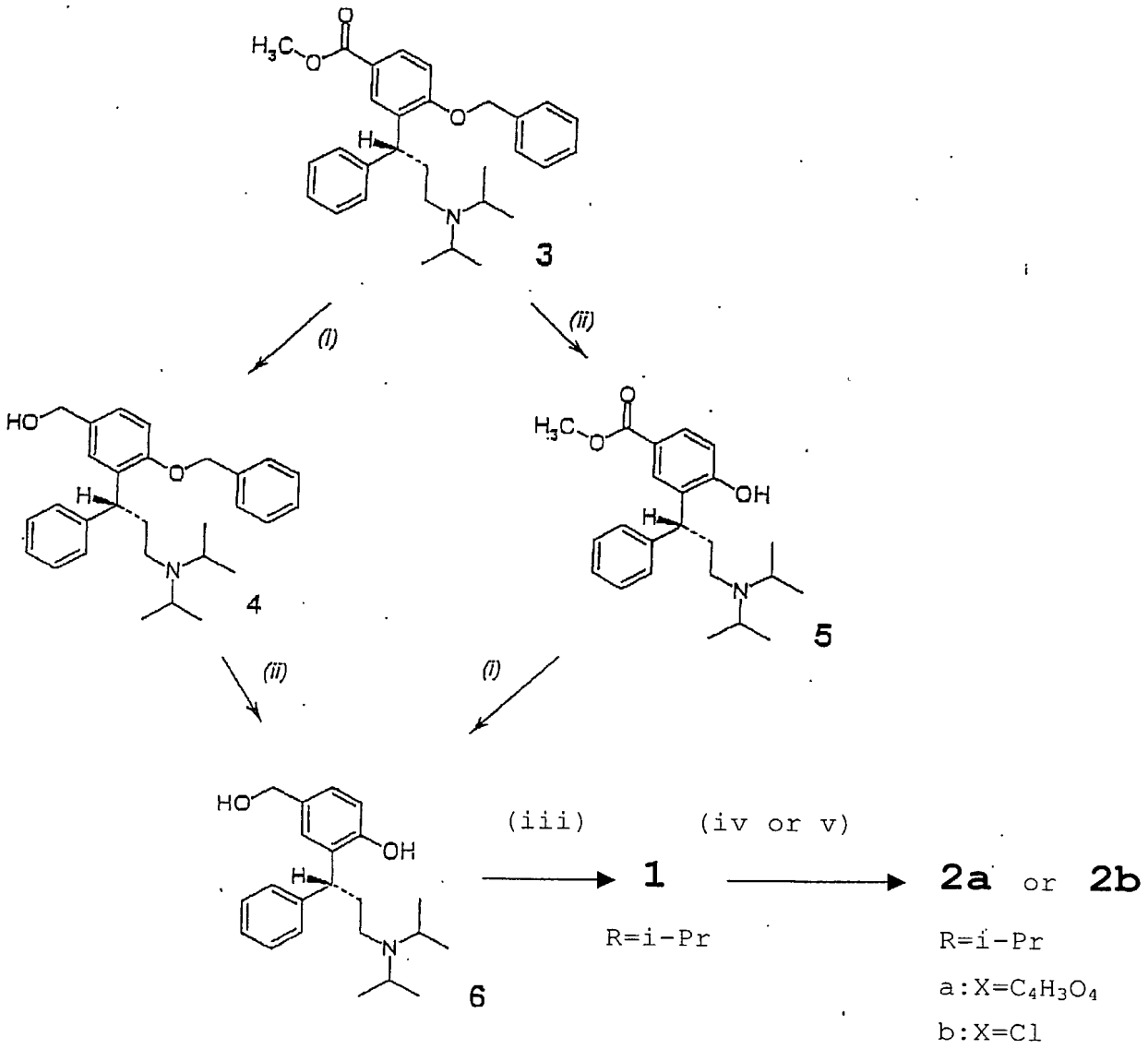
Formula 1

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl or unsubstituted or substituted phenyl.

Figure 1

Reaction diagram 1

(i), (ii), (iii), (iv), (v) stand for: (i), $LiAlH_4$, (ii), Raney nickel/H_2, (iii), Me_2CH-CoCl, Et_3N, (iv), fumaric acid, (v), hydrochloric acids; R stands for isopropyl (iPr)



SPECIFICATION

Stable salts of novel derivatives of 3,3-diphenylpropylamines

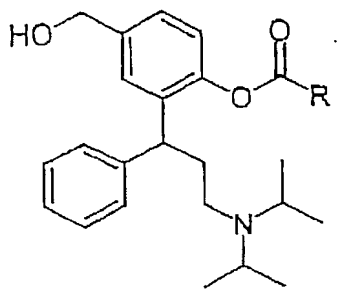
The present invention concerns highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, a method for manufacturing these and highly pure, stable, intermediate products.

From document PCT/EP99/03212 novel derivatives of 3,3-diphenylproprylamines are known.

These are valuable prodrugs for the treatment of urinary incontinence and other spasmodic complaints, which overcome the disadvantage of the active substances available to date, namely inadequate absorption of the active substance by biological membranes or the unfavourable metabolism of these.

Furthermore these novel prodrugs have improved pharmacokinetic characteristics compared with Oxybutynin and Tolterodin.

Preferred compounds from the group of these novel derivatives of 3,3-diphenylpropylamines are esters of aliphatic or aromatic carboxylic acids with the general formula A referred to below



Formula A

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl or unsubstituted or substituted phenyl. These can occur in their optical isomers form as racemic mixtures and in the form of their individual enantiomers.

Compounds with the structure of formula A do, however, have low solubility in water. This restricts their oral bioavailability.

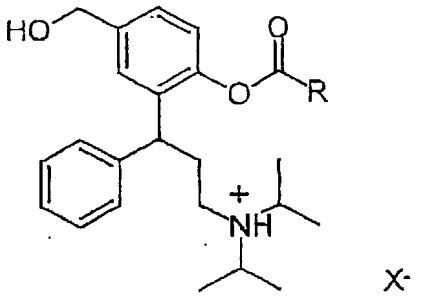
Finally, monoesters of the structure, as shown in formula A, have a tendency towards intermolecular transesterification.

During long periods of storage, therefore, as the content of the compounds with the structure of general formula A drops an increase in diesters and free diol can be detected.

Basically salts of the compounds of general formula A can be obtained if solutions of the compounds of formula A (base component) are purified with solutions of acids in suitable solvents, but the salts obtained in the form of solid matter can prove to be altogether amorphous and/or hygroscopic and cannot be directly crystallized from the normal solvents either. Such salts have inadequate chemical stability to be galenically processed as valuable pharmaceutically active substances.

Surprisingly, it has now been found that the abovementioned disadvantages can be avoided if compounds with the structure of general formula A, once they have been prepared under a special reaction process, are converted with a physiologically compatible inorganic or organic acid with general formula H-X, in which ^-X represents the respective

acid residue, into their respective salt with general formula I.



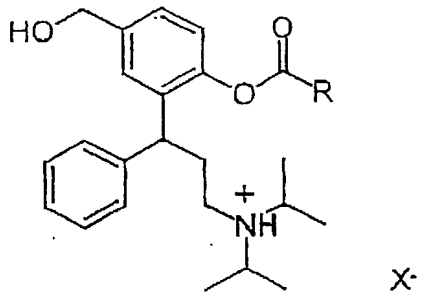
Formula I

The problem for the present invention is therefore to provide highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, that avoid the stated disadvantages and are well suited to use in pharmaceutical-technical formulations and can be processed into these.

A further problem for the present invention is to provide a method for manufacturing such highly pure, crystalline, stable compounds in the form of their salts, as well as highly pure, stable intermediate products.

The final problem for the invention is to provide a method for manufacturing the abovementioned compounds with which a high yield of the products of the process and the respective intermediate products can be obtained chemo- or regioselectively.

This problem is solved in that highly pure, crystalline, stable compounds of the 3,3-diphenylpropylamines in the form of their salts with general formula I are provided,



Formula I

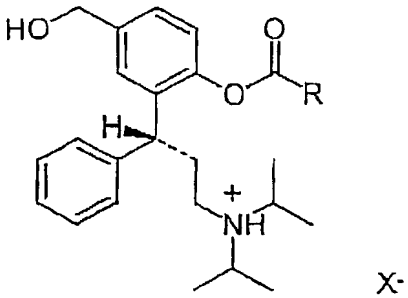
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

In accordance with a design of the invention the salts of general formula I can contain the respective acid residue X^- of the acids mentioned below:

hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid

(3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

In accordance with a further design form of the invention *R*-configured compounds with general formula 2 are provided



Formula 2

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

In accordance with an advantageous design form of the invention the compounds in the form of their salts of general formula 2 can contain the respective acid residue X^- of the acids mentioned below:

hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-

glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

Preferred compounds of the present invention are the salts

- *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate

- and

- *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate.

Furthermore, compounds are preferred in which R stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-(1-cyclopropyl-methanoyloxy)-phenyl, 4-(1-cyclobutyl-methanoyloxy)-phenyl, 4-(1-cyclohexyl-methanoyloxy)-phenyl or 4-(2,2-dimethyl-propanoyloxy)-phenyl and X^- denotes chloride.

Particular preference is for [(R)-3-(2-{1-[4-(1-cyclopropyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenylpropyl]-diisopropyl-ammonium chloride, [(R)-3-(2-{1-[4-(1-cyclobutyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium chloride, [(R)-3-(2-{1-[4-(1-cyclohexyl-methanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium chloride, [(R)-3-(2-{1-[4-(2,2-dimethyl-propanoyloxy)-phenyl]-methanoyloxy}-5-hydroxymethyl-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium chloride, {(R)-3-[2-(1-cyclopropyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride, {(R)-3-[2-(1-cyclobutyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-

propyl}-diisopropyl-ammonium chloride, {(R)-3-[2-(1-cyclopentyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride and {(R)-3-[2-(1-cyclohexyl-methanoyloxy)-5-hydroxymethyl-phenyl]-3-phenyl-propyl}-diisopropyl-ammonium chloride.

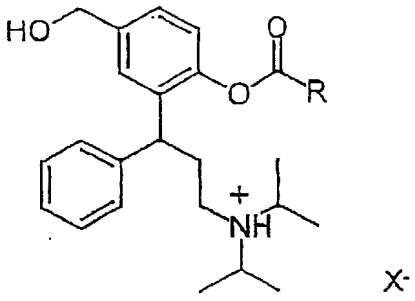
In the compounds of the present invention the expression "alkyl" preferably stands for a straight-chain or branched-chain hydrogen group with between 1 and 6 C-atoms. Special preference is for methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl and hexyl. The expression "cycloalkyl" designates cyclical hydrogen groups, that have between 3 and 10 hydrogen atoms, that may also contain suitable substitutes in place of the hydrogen atoms.

The expression "phenyl" designates a $-C_6H_5$-group that may be substituted or unsubstituted. Suitable substitutes can be, for example, alkyl, alkoxy, halogen, nitro and amine. The expression "alkoxy" has, with respect to the alkyl component, the same meaning as already given above for "alkyl". Suitable halogens are fluorine, chlorine, bromine and iodine atoms

The present invention also includes methods for manufacturing the compounds in accordance with the invention of general formula I as well as valuable intermediate products.

The method is characterised by chemo- and regioselectivity.

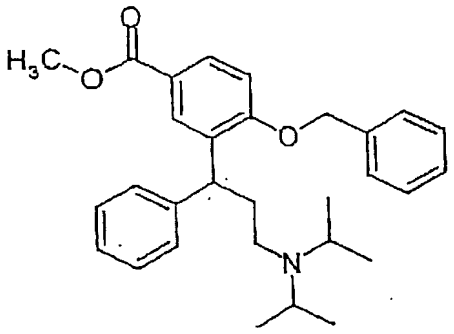
Compounds of general formula I



Formula I

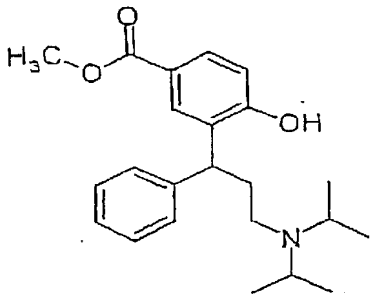
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid, are manufactured in that

a) a compound of formula III



Formula III

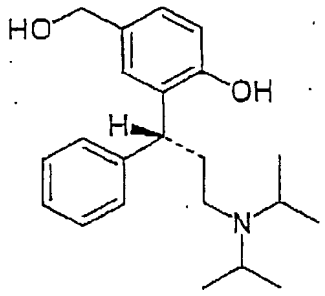
is split with a hydrogenation agent to form a compound of formula V



Formula V

whereupon

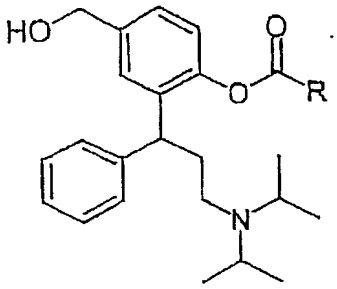
b) the compound of formula V so obtained is converted with a reducing agent, in order to give a compound of formula VI



Formula VI

which

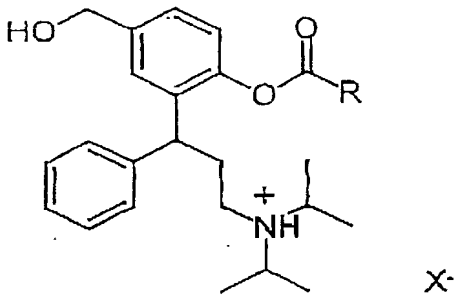
c) is converted with an acylation agent, in order to obtain a compound of formula A



Formula A

in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula I

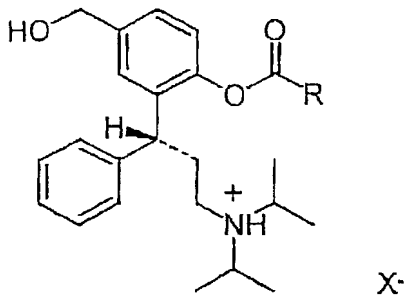


Formula I

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

In accordance with the invention, for the manufacture of the compounds of general formula I hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

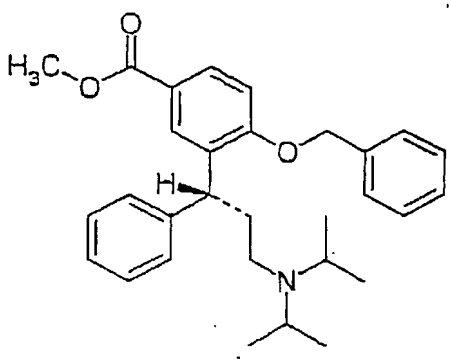
In accordance with an advantageous further development of the invention a method for the manufacture of *R*-configured compounds of the general formula 2 is described,



Formula 2

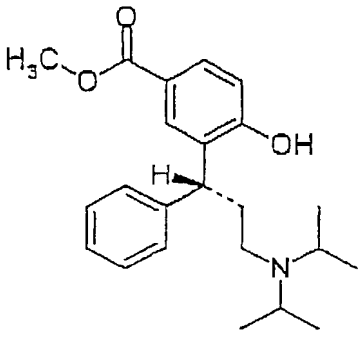
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid, in that

a) a compound of formula 3



Formula 3

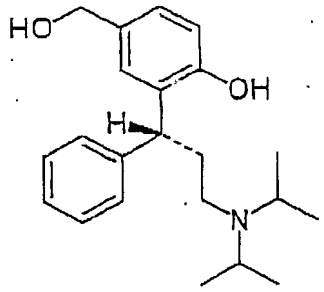
is split with a hydrogenation agent to form a compound of formula 5



Formula 5

whereupon

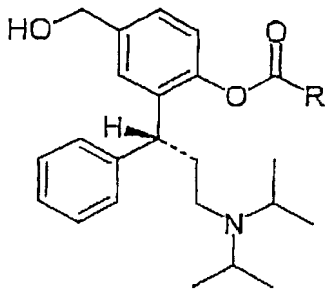
b) the compound of formula 5 so obtained is converted with a reducing agent, in order to give a compound of formula 6



Formula 6

which

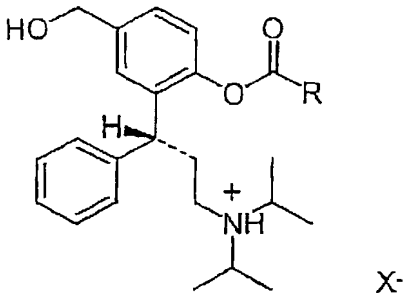
c) is converted with an acylation agent, in order to obtain a compound of formula 1



Formula 1

in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula 2



Formula 2

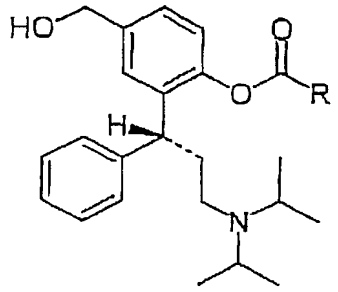
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, unsubstituted or substituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

Advantageously in order to obtain compounds of general formula 2, in accordance with the method hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

Particular advantageously, on the basis of the crystalline *R*-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)benzoic acid methyl ester, the highly pure,

crystalline intermediate product *R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester is prepared, which is reduced to *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol, is finally acylated in a suitable manner and is then converted with a physiologically compatible inorganic or organic acid under spontaneous crystallisation to the respective highly pure, crystalline, stable salt.

Depending on the acid chloride used, compounds of general formula 1 are obtained,



Formula 1

in which R denotes C_1-C_6-alkyl, in particular isopropyl, C_3-C_{10}-cycloalkyl or unsubstituted or substituted phenyl.

In order to obtain the compounds in accordance with the invention in the form of their salts the special reaction process via particular intermediate stages and individually identifiable intermediate products is crucial.

This is explained using reaction diagram 1 (see Figure 1), in which the conversions with *R*-configured compounds are described, but without this being restrictive.

In this:

3 = *R*-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid- methyl ester

4 = *R*-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol

5 = *R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester

6 = *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol

1 = *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester

2a = *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenyl-isobutyrate ester hydrogen fumarate

2b = *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydro xymethylphenyl-isobutyrate ester hydrochloride hydrate

In accordance with the reaction process explained in the embodiment the preliminary stage 3 (*R*-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid-methylester) is prepared in crystalline, pure form.

Using normal methods - such as BBr_3, $AlCl_3$ - but preferably by means of hydrogen gas via Raney nickel in methanol as the solvent at room temperature (RT), preliminary stage 3 is split into 5 (*R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methylester. This develops in highly pure, crystalline form (melting point 143.7 °C).

Finally, using a suitable reducing agent - such as $NaBH_4$/EtOH - preferably $LiAlH_4$ 5 is reduced into an inert solvent at low

temperature (-78°C to + 10°C) and the compound 6 (*R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol) is obtained. The compound 6 is obtained in a highly pure state and can be crystallised from a suitable solvent such as ethyl acetate. The colourless, compact grained material has a melting point of 102.3°C. This is surprising in that the compound 6 in the state of the art is described as an amorphous solid.

Compound 6 is now acylated with very good yield and regio- and chemoselectivity, into a phenolic ester. This reaction is performed at RT or low temperatures with an equivalent acid chloride in the presence of a base in a suitable solvent. Suitable solvents are ethyl acetate, dichloromethane, tetrahydrofurane, acetonitrile or toluene.

The reaction is preferably performed with isobutyrylchloride as the acid chloride and triethylamine as the base at the abovementioned temperatures. The 1 (*R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester) then obtained, occurs with such purity that with solutions of the fumaric acid in suitable solvents spontaneous crystallisation starts with the formation of the hydrogen fumarate salt 2a.

This salt has a high melting point of 103°C, is stable at RT, is non-hygroscopic and does not contain crystallose agents. It can be recrystallised as often as desired.

If instead of fumaric acid anhydrous hydrochloric acid is used - for example as an etheric solution - salt formation also takes place with the crystalline product 2b (*R*-(+)-2-(3-

diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester hydrochloride hydrate being obtained.

Following a further recrystallisation the product 2b has a melting point range of 97 - 106°C.

Finally the product 2b can particularly advantageously be obtained by the following variants of the inverse reaction process, starting with the compound 6 of reaction diagram 1. The product 2b can thus be obtained without the addition of an external acid-intercepting base, as explained in the following.

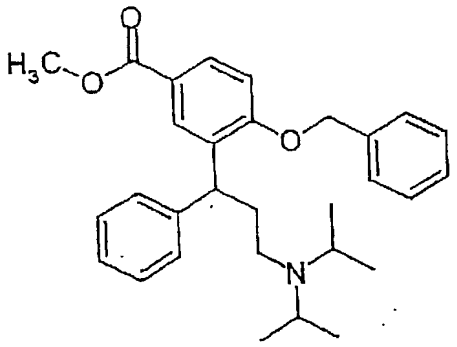
Solutions of 6 (*R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol) are dripped into solutions of isobutyrate chloride, so that under suitable polarity conditions the anhydrous product 2b rapidly crystallises out. 2b is very hygroscopic.

If the abovementioned reaction is carried out in a humid solvent, that contains at least one mole equivalent of water, a stable and crystalline, hydrate-containing product 2b is obtained, that has the abovementioned melting characteristics.

The compounds in accordance with the invention of general formulae 1 and 2 are suited to bulk material.

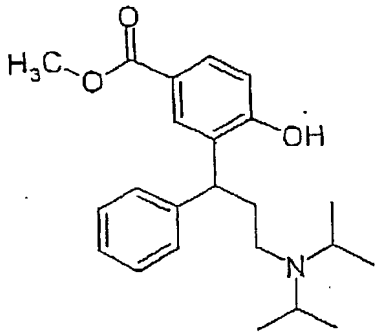
Of particular advantage are the highly pure compounds of general formulas III, V, VI, 3, 5, 6 and 7 which can be obtained.

Compound of formula III



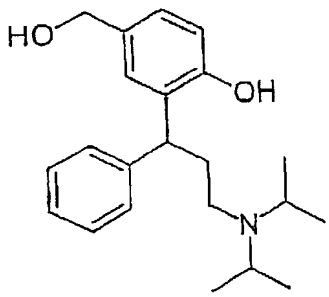
Formula III

Compound of formula V



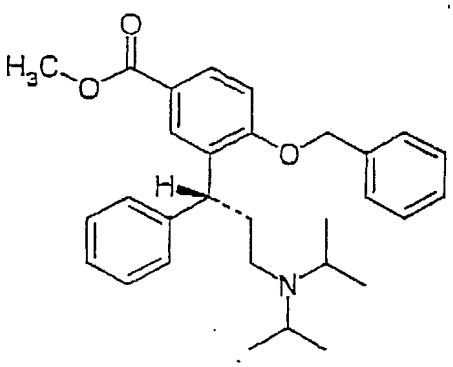
Formula V

Compound of formula VI



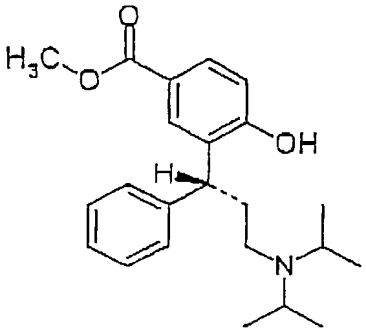
Formula VI

Compound of formula 3



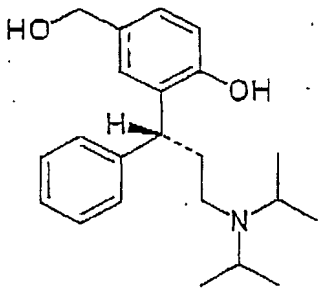
Formula 3

Compound of formula 5



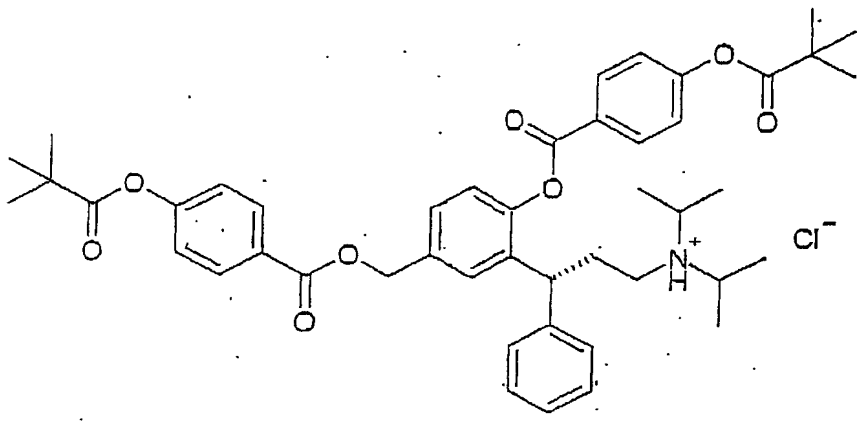
Formula 5

Compound of formula 6



Formula 6

Compound of formula 7



Formula 7

[(R)-3-(2-{1-[4-(2,2-dimethyl-propanoyloxy)-phenyl]-methaneoyloxy}-5-{1-[4-(2,2-dimethyl-propanoyloxy)-phenyl]-methaneoyloxymethyl}-phenyl)-3-phenyl-propyl]-diisopropyl-ammonium-chloride

The abovementioned compounds III, V, VI, 3, 5, 6 and 7 are particularly suited to use in each case as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds.

Of particular advantage are compounds for use as an intermediate product in the manufacture of *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate and *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate.

Finally, the method can be carried out in a particularly advantageous way by converting a compound of general formula 6 (see reaction diagram 1) with an equivalent isobutyryl

chloride in the presence of triethylamine using one of the respective solvents ethylacetate, dichloromethane, tetrahydrofurane, acetonitrile or toluene regio- and chemoselectively into *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester.

In accordance with the invention *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester is particularly suited to conversion with fumaric acid or hydrochloric acid with the formation of the respective salt.

The following embodiments explain the invention.

Experimental

I. General

All compounds have been fully characterised by ^{1}H and ^{13}C NMR-spectroscopy (Bruker DPX 200). The stated chemical displacements in the ^{13}C-NMR-spectra (50 MHz, ppm values stated) refer to the solvent resonances of $CDCl_3$ (77.10 ppm). ^{1}H NMR data ($CDCl_3$; 200 MHz, ppm) refer to internal tetramethylsilane).

Thin layer chromatography (DC, R_f given) was carried out on 5x10 cm E. Merck silica gel films (60F254), and the stains were revealed by fluorescence erasure or by spraying with alkaline potassium permanganate solution.

Absorbent systems were: (1), n-hexane / acetone / triethylamine (70/20/10, v/v-%); (2), toluene / acetone / methanol / acetic acid (70/5/20/5, v/v-%).

The optical rotations were measured at a wavelength of 589.3 nm (sodium D-line), at room temperature using ethanol as a solvent (apparatus: Perkin Elmer Polarimeter Type 241), melting points (in °C) are uncorrected and were determined on the Mettler FP apparatus, or by differential thermoanalysis (DSC) on the Perkin Elmer Model DSC7, using "Pyris" evaluation software.

UV/VIS measurements were carried out on the spectrophotometer model Lambda 7 (Perkin-Elmer) with a layer thickness of 1 cm. The specific absorption stated is for a 1% solution ($A^{1\%}_{1\ cm}$).

IR spectra were recorded on a Perkin-Elmer FTIR spectrometer Series 1610 (resolution 4 cm^{-1}).

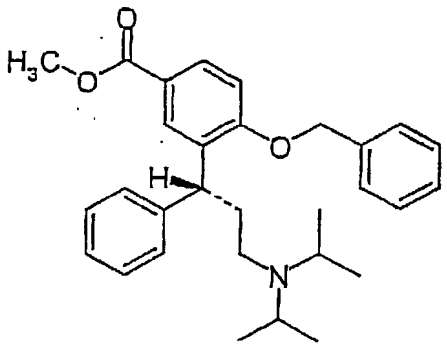
Gas chromatography mass spectrometry (GC-MS, m/z values and relative intensity with reference to the base ion (%)) was carried out with a Finnigan TSQ 700 Triple Mass Spectrometer in positive (P-CI) or negative (N-CI) chemical ionisation measurement mode with methane or ammonium as a reactant gas or via electron impact ionisation. Hydroxy compounds were measured as trimethylsilylether-derivatives.

Coupled liquid chromatography-mass spectrometry (LC-MS): Waters Integrity System, Thermabeam Mass Detector (EI, 70 eV), m/z-values and relative intensity (%) are given over a quantity range of 50-500 a.m.u.

II. Embodiments

The Arabic numerals in brackets (3), (4), (5), (6) refer to the identical designations in reaction diagram 1.

1. Preparation of
R-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid methylester (3)



A solution of *R*-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid hydrochloride (2.30 kg, 4.77 Mol) in 26.4 litres of methanol and 0.25 litre of concentrated sulphuric acid is heated for 16 hours with recycling. Then a third of the solvent is distilled off, cooled and under agitation mixed with 5 kg ice and 2.5 litres 25% aqueous sodium carbonate solution. The deposit is first extracted with 15 litres and then again with 5 litres of dichloromethane. The organic phases are purified and concentrated on the rotary evaporator until dry. 1.99 kg (90.7% of theoretical) dark yellow oil with a purity of approximately 90% (DC, NMR) are obtained.
DC (1): 0.58

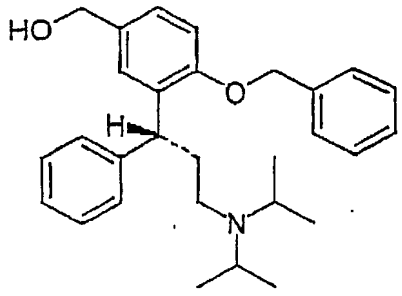
^{13}C-NMR ($CDCl_3$): 20.55, 20.65, 36.83, 41.84, 43.83, 51.82, 70.12, 111.09, 122.46, 125.28, 127.49, 128.02, 128.35, 128.50, 129.22,129.49, 133.20, 136.39, 144.51, 159.87, 167.09.

Recrystallisation

69.0 oily raw material is dissolved in 150 ml boiling methanol. Following the addition of 15 ml distilled water it is left at 0°C, whereupon colourless crystals precipitate. These are filtered off, washed with a little cold methanol and vacuum-dried. Yield: 41.8 g (60.6 % of theoretical) colourless crystals, melting point 89.8 °C; $[I]_D^{20}$ = - 30.7 (c = 1.0, ethanol).

2. Preparation of

R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (4)



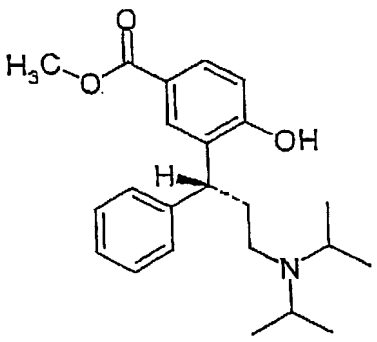
Raw product (3) (28 g) is dissolved in 230 ml pure diethylether and under agitation is dripped into a suspension of 1.8 g lithium-aluminium hydride in diethylether (140 ml). After 18 hours of agitation at room temperature, 4.7 ml of water are added in drop form. The organic phase is separated

off, dried with anhydrous sodium sulphate, filtered and concentrated on the rotary evaporator until dry. 26 g (98.9% of theoretical) *R*-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (4) are obtained as a colourless oil.

DC (2): 0.32; $[I]_D^{20}$ = + 6.3 (c = 1.0, ethanol).

^{13}C-NMR ($CDCl_3$): 20.53, 20.61, 36.87, 41.65, 44.14, 48.82, 65.12, 70.09, 111.80, 125.77, 125.97, 126.94, 127.55, 128.08, 128.37, 128.44, 133.27, 134.05, 134.27, 137.21, 144.84.

3. Preparation of
R-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester (5)



To an agitated suspension of 5g Raney nickel (washed with water, then with methanol) in 200 ml methanol, 10 g (21.8 mmol) *R*-(-)-4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-benzoic acid methyl ester (3) are added. Following brief heating, in order to dissolve all (3) completely, the apparatus is placed under a hydrogen gas atmosphere. After three hours of agitation at normal pressure and room temperature, the thin layer chromatography demonstrates

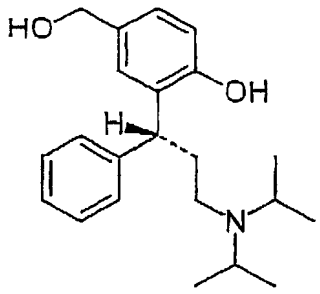
complete conversion. The deposit is rinsed with nitrogen gas and following addition of some active charcoal is filtered. Following concentration of the methanolic solution on the rotary evaporator 6.0 g (75% of theoretical) *R*-(-)-3-(3-diisopropylaminophenyl-propyl)-4-hydroxy-benzoic acid methyl ester (5) remains in the form of colourless crystals with a purity of 99.6 % (HPLC).

Melting point 143.7 °C; DSC 144.7°C

$[I]_D^{20}$ = -26.6 (c = 0.93, ethanol).

^{13}C-NMR ($CDCl_3$): 18.74, 19.21, 19.62, 33.12, 39.68, 42.36, 48.64, 51.42, 117.99, 120.32, 126.23, 127.81, 128.85, 129.39, 130.26, 132.21, 144.06, 162.43, 167.35.

4. Preparation of
R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6)



a) Starting from the intermediate stage (4), *R*-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol

R-(+)-[4-benzyloxy-3-(3-diisopropylamino-1-phenyl-propyl)-phenyl]-methanol (19.7 g, 45.7 mmol) are dissolved in 220 ml methanol and Raney nickel (5 g). The apparatus is rinsed with hydrogen gas and the deposit is agitated for two days at room

temperature. Following the addition of a further 5 g Raney nickel, agitation for a further two days at room temperature takes place under a hydrogen gas atmosphere, followed by filtration off from the catalyser and concentration until dry on the rotary evaporator. The oily, pale yellow residue is dissolved in 100 ml diethylether, washed twice with 100 ml water each time, dried via sodium sulphate, filtered and concentrated until dry. 14.1 g (90.4% of theoretical) *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol are obtained in the form of a cream-coloured, amorphous solid. For recrystallisation see under c).

b) Starting from the intermediate stage (5); *R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester

A solution of 370 mg (1.0 mmol) *R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester in 20 ml anhydrous tetrahydrofurane is slowly and at room temperature dropped into an agitated mixture of dried tetrahydrofurane (10 ml) and a 1M solution of lithium-aluminium hydride in tetrahydrofurane (3 ml) (under a nitrogen protective gas atmosphere). Excess hydride is decomposed by the dropped addition of a saturated sodium carbonate solution. Following separation of the organic phase this is concentrated on the rotary evaporator and then dried in the high-vacuum. 274 mg (74% of theoretical) pale yellow oil is obtained, that slowly solidifies into an amorphous mass.

c) Recrystallisation:

Raw product 6 (1.0 g) is dissolved in ethyl acetate and again concentrated on the rotary evaporator. The diol released in

this way from foreign solvents (diethyl ether or tetrahydrofurane, see above) has 1.5 ml ethyl acetate added with slight heating. Agitation takes place until a clear solution results, followed by cooling at room temperature and addition of a few seed crystals. These are obtained by purifying raw 6 via HPLC, collecting the main fraction, concentrating this and drying the residue for a number of hours in the high-vacuum. Once clear crystallisation has definitely started, it is left at - 10°C. The crystals are sucked off in the cold and dried in the vacuum. Colourless crystals with a yield of 84% are obtained.

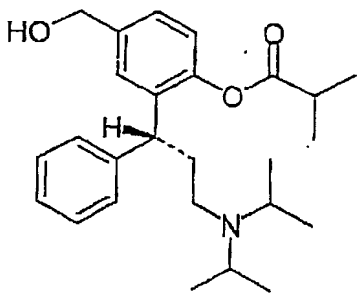
Melting point 102.3 °C

DC (1): 0.57

$[I]_D^{20}$ = +21.3 (c = 1.0, ethanol).

^{13}C-NMR ($CDCl_3$): 19.58, 19.96, 33.30, 39.52, 42.10, 48.00, 65.40, 118.58, 126.31, 126.57, 127.16, 127.54, 128.57, 132.63, 132.83, 144.55, 155.52.

5. Preparation of
R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenolisobutyrate ester (1)

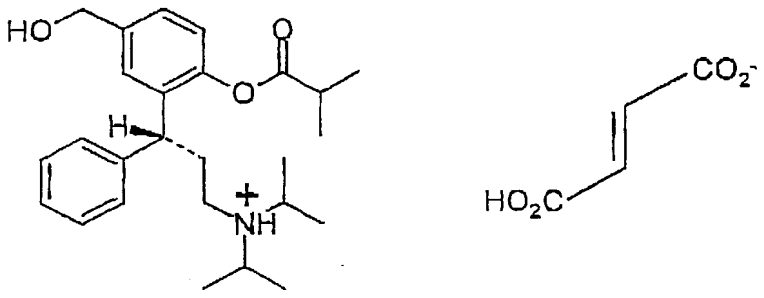


A solution of *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenol (6) (65.0 g, 190.3 mmol) and triethylamine (20.4 g, 201.7 mmol) in 750 ml dichloromethane has a solution of isobutyrate chloride (23.4 g, 201.7 mmol) in 250 ml dichloromethane added under agitation and cooling. Following addition agitation takes place for a further 15 minutes at 0°C, then for 30 minutes at room temperature and then one after another washing with water (250 ml) and 5% aqueous sodium hydrogen carbonate solution. The organic phase is separated and concentrated on the rotary evaporator until dry. The ester *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester is obtained as a colourless, viscous oil; yield: 77.1 g (98.4 % of theoretical).

DC (1): 0.26; $[I]_D^{22}$ = + 2.7 (c = 1.0, ethanol).

^{13}C-NMR ($CDCl_3$):19.01, 19.95, 20.59, 21.12, 34.28, 36.89, 41.88, 42.32, 43.90, 48.78, 64.68, 122.57, 125.59, 126.16, 126.86, 127.96, 128.54, 136.88, 138.82, 143.92, 147.90, 175.96.

6. Preparation of
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobutyrate ester hydrogen fumarate.



A solution of 41.87 g (102 mmol) *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester in 90 ml 2-butanone has fumaric acid (11.81 g, 102 mmol) added while heating. Following dissolution of the acid, cyclohexane (20-30 ml) is slowly added under agitation until the onset of turbidity. The colourless, homogenous deposit is initially left for 18 hours at room temperature, and then for several hours at 0°C. The colourless crystals that have precipitated are sucked off, washed with a little cyclohexane/2-butanone (90:10, vol.-%)and dried in the vacuum at 30°C. 44.6 g (83.1 % of theoretical) hydrogen furate salt of *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenyl-isobutyrate ester in the form of colourless flakes are obtained.

Melting point 98.8°C, a second crystallisation from the same solvent mixture provides a product with a melting point of 103°C.

$[I]_D^{20}$ = +6.0 (c = 1.0, ethanol).

Elementary analysis: Calculated for $C_{30}H_{41}NO_7$ (molecular weight 527.66) C 68.29 %, H 7.83 %, N 2.65 %, O 21.2 %; found C 68.29 %, H 7.90 %, N 2.72 %, O 21.0 %.

UV/VIS at Σ in nm ($A^{1\%}_{1\ cm}$): 191 (1306), 193 (1305), 200 (1143), 220 (456).

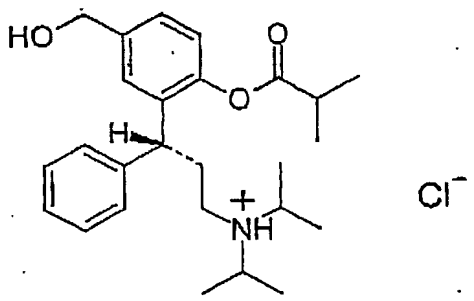
IR: 3380, 2978, 2939, 2878, 2692, 2514, 1756, 1702, 1680, 1618, 1496, 1468, 1226, 1040, 1019, 806,

^{1}H-NMR ($CDCl_3$): 1.198, 1.285, 1.287 (CH_3); 2.541 (CHC=O); 3.589 (NCH); 4.585 ($\underline{C}H_2OH$); 6.832 (=CH, fumarate); 6.84-7.62 (aryl, = CH).

^{13}C-NMR ($CDCl_3$): 17.79, 18.95, 19.16 (CH_3); 31.63 ($CH\underline{C}H_2$); 34.09 ($\underline{C}H$-C=O); 41.87 ($CH\underline{C}H_2$); 45.83 (NCH_2); 54.29 (NCH); 63.78 (OCH_2); 122.23, 126.48, 126.77, 127.56, 140.46, 140.52, 142.35, 147.54 (Aryl CH); 135.54 (=CH, fumarate); 170.48 (C=O, fumarate); 175.62 (i-Pr-C=O).

MS in the direct inlet, m/z (%): 411 (1), 396 (9), 380 (1), 223 (2), 165 (2), 114 (100), 98 (4), 91 (3), 84 (3), 72 (10), 56 (7).

7. Preparation of
R-(+)-2-(3-Diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobutyrate ester hydrochloride hydrate



A solution of *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester (8.54 g, 25.0 mmol) in 50 ml dichloromethane is slowly dropped at 0°C into an agitated solution of isobutyrate chloride (2.66 g, 25.0 mmol) in 100 ml dichloromethane. After an hour the cooling is

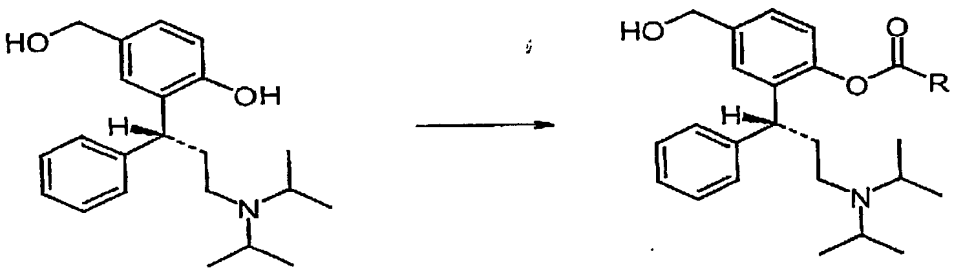
removed and re-agitation takes place for an additional hour. Following the drawing off of the volatile components in the vacuum on the rotary evaporator a colourless, amorphous-solid foam remains. This residue is dissolved in acetone (17 ml), with 0.45 to 0.50 g water and diethyl ether is added (approx. 20 - 25 ml) until there is a definite onset of turbidity. Following brief treatment with ultrasound crystallisation starts spontaneously and under agitation a further 80 ml of diethyl ether are slowly added. The precipitated colourless crystals are sucked off and dried overnight in the vacuum via phosphorous pentoxide. 10.5 g (93.7 % of theoretical) colourless crystalline *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate with a purity of 97.0% (HPLC) are obtained.

Melting point 97.1 °C.

$[I]_D^{20}$ = + 4.3 (c = 1.03, ethanol)

^{13}C-NMR ($CDCl_3$): 16.94, 17.35, 18.24, 18.40, 18.87, 19.05, 31.20, 33.99, 41.64, 45.41, 54.18, 54.42, 63.83, 122.25, 126.50, 126.70, 126.96, 127.34, 128.60, 133.80, 140.55, 142.17, 147.68, 175.79.

8. Phenolic monoester



General work specification for the manufacture of phenolic monoesters

Into a solution of 120.3 mg (0.352 mmol) R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxyphenol (6) in 5 ml dichloromethane, under agitation at 0°C, a solution of acid chloride (0.352 mmol) in 2 ml dichloromethane is dropped. Then triethylamine-dichloromethane (49.1µl/0.353 mmol-2 ml) is added. After 18 hours at room temperature the thin layer chromatography shows that conversion is complete. The deposit is washed successively with 5 ml water, aqueous 0.1N-hydrochloric acid, 5 ml 5% aqueous sodium-hydrogen carbonate solution, 5 ml water, dried via sodium sulphate and following filtration concentrated until dry. Then it is dried in the high-vacuum until constant weight.

The following compounds are, by way of example, manufactured using this method:

R = $CH_2CH(CH_3)_2$

R-(+)-3-methylbutyric acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester

Colourless oil with 70% yield and >95% purity (NMR).
^{13}C-NMR ($CDCl_3$): 20.45, 20.59, 22.54, 25.70, 36,74, 42.18, 43.27, 43.96, 48.90, 64.67, 122.66, 125.60, 126.20, 126.79, 127.95, 128.37, 136.83, 138.86, 143.83, 147.82, 171.37.
DC (1): 0.76.

R = $CH_2C(CH_3)_3$

R-(+)-3.3-dimethylbutyric acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester, free base

Colourless oil with 69.7% yield and >95% purity (NMR).
^{13}C-NMR ($CDCl_3$): 20.40, 20.53, 29.73, 30.99, 36.62, 42.17, 44.01, 47.60, 49.01, 64.65, 122.64, 125.60, 126.20, 126.80, 127.96, 128.36, 136.85, 138.90, 143.80, 147.82, 170.55.
DC (1): 0.75.

R = $(CH_3)_3C$

R-(+)-3-pivalic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride.

Colourless crystals, melting point 165-6 °C.
^{13}C-NMR (DMSO-d_6 =39.7 ppm): 16.52, 16.68, 17.98, 18.11, 26.87, 31.46, 41.71, 45.33, 53.89, 53.98, 62.65, 122.61, 122.97, 125.94, 126.09, 126.57, 126.75, 127.87, 128.58, 131.80, 134.94, 141.02, 142.69, 147.17, 155.32, 163.92, 176.21.

R = c-C_3H_5

R-(+)-cyclopropane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride.

Colourless, waxy substance.

^{13}C-NMR (DMSO-d_6 =39.7 ppm): 173.02, 172.49, 172.37, 153.10, 147.12, 142.72, 142.03, 140.78, 136.60, 134.79, 134.35, 129.55, 129.13, 128.80, 128.67, 127.87, 126.96, 126.74, 125.94, 125.84, 124.37, 123.71, 122.80, 62.64, 53.92, 45.34, 41.65, 31.44, 18.05, 16.66, 12.84, 9.58, 9.28, 8.49, 7.89.

R = c-C_4H_7

R-(+)-cyclobutane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride

Colourless, waxy substance.
^{13}C-NMR (DMSO-d_6 =39.7 ppm): 173.53, 147.12, 142.81, 140.74, 134.77, 128.65, 127.81, 126.74, 125.99, 125.87, 122.75, 62.63, 53.92, 45.34, 41.42, 37.38, 31.54, 25.04, 24.92, 18.03, 16.68, 16.61.

R = c-C_5H_9

R-(+)-cyclopentane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride

Colourless, waxy substance.
^{13}C-NMR (DMSO-d_6 =39.7 ppm): 174.80, 147.22, 142.86, 140.76, 134.72, 128.66, 127.80, 126.73, 126.04, 125.88, 122.71, 62.62, 53.94, 45.37, 43.24, 41.39, 31.54, 29.78, 29.59, 25.64, 25.59, 18.07, 16.64.

R = c-C_6H_{11}

R-(+)-cyclohexane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride

Colourless, waxy substance.
^{13}C-NMR (DMSO-d_6 =39.7 ppm):
174.08, 147.15, 142.85, 140.77, 134.78, 128.66, 127.77, 126.74, 126.06, 125.87, 122.69, 62.61, 53.91, 45.36, 42.26, 41.24, 31.53, 28.74, 28.62, 25.48, 25.04, 24.98, 18.05, 16.67, 16.60.

R = 4-($C_2H_5CO_2$)-C_6H_4

R-(+)-4-ethylcarbonyloxy-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester
hydrochloride

Colourless crystals, melting point 195-8 °C.
^{1}H-NMR (DMSO-d_6): 9.87 (s, 1H can be substituted with D_2O, NH), 8.19-8.12 (m, 2H, Phenyl-H), 7.55 (d, J = 1.0 Hz, 1H, Phenyl-H3), 7.41-7.13 (m, 9H, Phenyl-H), 5.28 (br s, 1H can be substituted with D_2O, OH), 4.53 (s, 2H, CH_2), 4.23 (t, J = 7.6 Hz, 1H, CH), 3.61-3.50 (m, 2H, 2 × C<u>H</u>$(CH_3)_2$), 2.97-2.74 (m, 2H, CH_2), 2.67 (q, J = 7.4 Hz, 2H, CH_2), 2.56-2.43 (m, 2H, CH_2), 1.23-1.13 (m, 15H, 2 × CH(C<u>H</u>$_3)_2$, CH_3).

R = 4-(i-$C_3H_7CO_2$)-C_6H_4

R-(+)-4-(isopropylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 202-4 °C.
^{1}H-NMR (DMSO-d_6): 9.73 (s, 1H can be substituted with D_2O, NH), 8.19-8.12 (m, 2H, Phenyl-H), 7.55 (d, J = 1.4 Hz, 1H, Phenyl-H3), 7.42-7.14 (m, 9H, Phenyl-H), 5.27 (br s, 1H can be substituted with D_2O, OH), 4.53 (s, 2H, CH_2), 4.23 (t, J = 7.5 Hz, 1H, CH), 3.61-3.50 (m, 2H, 2 × C<u>H</u>$(CH_3)_2$), 2.99-2.78 (m, 3H, CH_2, C<u>H</u>$(CH_3)_2$), 2.54-2.47 (m, 2H, CH_2), 1.29-1.13 (m, 18H, 3 × CH(C<u>H</u>$_3)_2$).

R = 4-(t-$C_4H_9CO_2$)-C_6H_4

R-(+)-4-(t-butylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester, free base.

Colourless oil.
^{1}H-NMR (DMSO-d_6): 8.19-8.12 (m, 2H, phenyl-H), 7.45-7.33 (m, 3H, phenyl-H), 7.25-7.09 (m, 7H, phenyl-H), 5.20 (t, J = 5.6 Hz, 1H, OH), 4.50 (d, J = 5.6 Hz, 2H, CH_2), 4.20 (t, J = 7.5 Hz, 1H, CH), 2.95-2.80 (m, 2H, 2 × C<u>H</u>$(CH_3)_2$), 2.38-2.25 (m, 2H, CH_2), 2.09-2.03 (m, 2H, CH_2), 1.33 (s, 9H, $(CH_3)_3$), 0.82-0.76 (m, 12H, 2 × CH(C<u>H</u>$_3)_2$).

Hydrochloride: colourless crystals, melting point 165-6 °C.
^{1}H-NMR ($CDCl_3$): 8.22-8.16 (m, 2H, phenyl-H), 8.02 (d, J = 1.8 Hz, 1H, phenyl-H), 7.27-7.02 (m, 9H, phenyl-H), 4.83-4.60

('m', 2H, CH_2), 4.01-3.94 (m, 1H, CH), 3.66-3.54 (m, 2H), 3.18-2.80 (m, 3H), 2.53-2.44 (m, 1H) (2 × CH_2, 2 × $C\underline{H}(CH_3)_2$), 1.43-1.25 (m, 21H, $(CH_3)_3$, 2 × $CH(C\underline{H_3})_2$).

R = 4-(c-$C_3H_5CO_2$)-C_6H_4

R-(+)-4-(cyclopropylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 208-213 °C.
^{1}H-NMR (DMSO-d_6): 9.04 (s, 1H can be substituted with D_2O, NH), 8.15-8.09 (m, 2H, phenyl-H), 7.53 ('d', 1H, phenyl-H3), 7.42-7.13 (m, 9H, phenyl-H), 5.25 (br s, 1H can be substituted with D_2O, OH), 4.52 (s, 2H, CH2), 4.23 (t, J = 7.5 Hz, 1H, CH), 3.62-3.53 (m, 2H, 2 × CH(CH3)2), 3.05-2.70 (m, 2H, CH2), 2.51-2.37 (m, 2H, CH2), 2.01-1.89 (m, 1H, cyclopropyl-CH), 1.20-1.05 (m, 16H, 2 × CH(CH3)2, 2 × cyclopropyl-CH2).

^{13}C-NMR (DMSO-d_6 =39.7 ppm): 172.71, 163.93, 154.92, 147.16, 142.69, 141.03, 134.97, 131.76, 128.60, 127.86, 126.76, 126.56, 126.06, 125.94, 122.95, 122.65, 62.65, 54.00, 53.89, 45.33, 41.63, 31.49, 18.10, 17.98, 16.69, 16.51, 12.86, 9.52.

R = 4-(c-$C_4H_7CO_2$)-C_6H_4

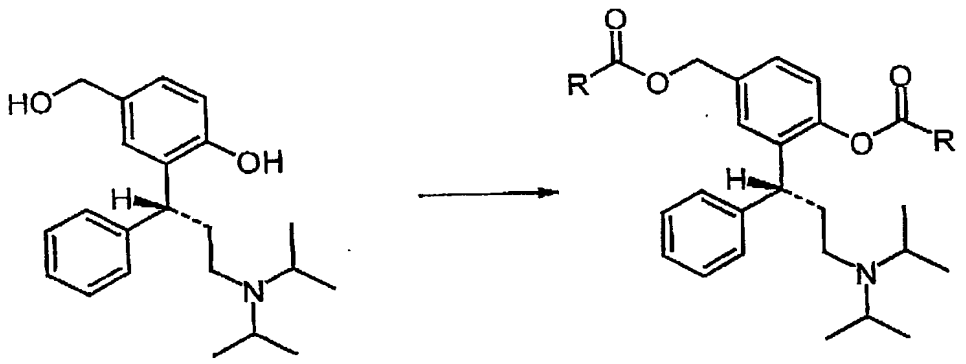
R-(+)-4-(cyclobutylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 201-6 °C.
^{1}H-NMR (DMSO-d_6): 9.50 (s, 1H can be substituted with D_2O, NH), 8.17-8.12 (m, 2H, phenyl-H), 7.54 (d, J = 1.4 Hz, 1H, phenyl-H3), 7.42-7.14 (m, 9H, phenyl-H), 5.25 (br s, 1H can be substituted with D_2O, OH), 4.52 (s, 2H, CH_2), 4.23 (t, J = 7.5 Hz, 1H, CH), 3.62-3.47 (m, 3H, cyclobutyl-CH), 2 × $C\underline{H}(CH_3)_2$), 3.00-2.70 (m, 2H, CH_2), 2.51-2.26 (m, 6H, CH_2, 2 × cyclobutyl-CH_2), 2.10-1.85 (m, 2H, cyclobutyl-CH_2), 1.22-1.12 (m, 12H, 2 × $CH(C\underline{H}_3)_2$).

R = 4-(c-$C_6H_{11}CO_2$)-C_6H_4
R-(+)-4-(cyclohexylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenyl-ester hydrochloride

Colourless crystals, melting point 212-217 °C.
^{1}H-NMR (DMSO-d_6): 9.34 (s, 1H, *can be substituted with D_2O*, NH), 8.16-8.12 (m, 2H, phenyl-H), 7.54 (d, J = 1.4 Hz, 1H, phenyl-H3), 7.39-7.14 (m, 9H, Phenyl-H), 5.26 ('t', 1H, *can be substituted with D_2O*, OH), 4.53 (d, J = 4.2 Hz, 2H, CH_2), 4.22 (t, J = 7.5 Hz, 1H, CH), 3.62-3.48 (m, 2H, 2 × $C\underline{H}(CH_3)_2$), 3.00-2.60 (m, 3H, cyclohexyl-CH), CH_2), 2.51-2.40 (m, 2H, CH_2), 2.07-1.98 (m, 2H, cyclohexyl-CH_2), 1.80-1.11 (m, 20H, 4 × cyclohexyl-CH_2), 2 × $CH(C\underline{H}_3)_2$)

9. Identical diesters



General work specification for the manufacture of identical diesters

Into a solution of 7.30 g (21.4 mmol)R-(+)-2-(3-diiso-propylamino-1-phenylpropyl)-4-hydroxyphenol (6) in 100 ml dichloromethane, under agitation at 0°C, a solution of acid chloride (49.2 mmol) in 50 ml dichloromethane is dropped. Then triethylamine-dichloromethane (6.86 ml/ 49.2 mmol-50 ml)is added. After 1-3 hours at room temperature the thin layer chromatography shows that conversion is complete. The deposit is washed successively with respectively 100 ml water, aqueous 0.1N-hydrochloric acid, 5 ml 5% aqueous sodium-hydrogen carbonate solution, 5 ml water, dried via sodium sulphate and following filtration concentrated until dry. Then it is dried in the high-vacuum until constant weight.

The following compounds are, by way of example, manufactured using this method:

R = Methyl

R-(-)-acetic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-acetoxymethyl-phenyl-ester, free base

Pale yellow oil, purity (HPLC): 95.2%.
^{13}C-NMR ($CDCl_3$): 20.36, 20.69, 20.94, 20.99, 36.41, 42.27, 43.69, 48.79, 65.89, 122.89, 126.28, 127.17, 127.92, 128.36, 133.69, 136.95, 143.61, 148.46, 168.97, 170.76.
LC-MS: 425 (15%, $M^{+\cdot}$), 410 (97%), 382 (4%), 308 (3%), 266 (7%), 223 (27%), 195 (13%), 165 (8%), 114 (100%).
$[\alpha]_D^{20}$ = -33.1 (c = 1, CH_3CN).
DC (1): 0.79.

R = Cyclohexyl

R-(+)-cyclohexane carboxylic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-cyclohexylcarbonyloxymethyl-phenyl-ester

Pale yellow oil, purity (NMR): >95%.
^{13}C-NMR ($CDCl_3$): 20.30, 25.17, 25.58, 25.73, 28.97, 29.12, 41.70, 43.15, 44.03, 48.64, 65.37, 122.67, 125.88, 126.24, 127.06, 127.31, 127.90, 128.37, 134,03, 136.85, 143.55, 148.33, 174.20, 175.72.
DC (1): 0.96.

R = Isopropyl

R-(+)-isobutyrate-2-(3-diisopropylamino-1-phenyl-propyl)-4-isobutyryloxymethyl-phenyl-ester

Free base: pale yellow oil, purity (HPLC): 95.6%.
^{13}C-NMR ($CDCl_3$): 18.96, 19.08, 20.59, 33.98, 34.20, 36.86, 41.72, 43.72, 48.72, 65.58, 122.65, 126.19, 126.73, 127.91, 128.11, 128.36, 133.91, 136.96, 143.81, 148.41, 175.15, 176.77.
DC (1): 0.74.

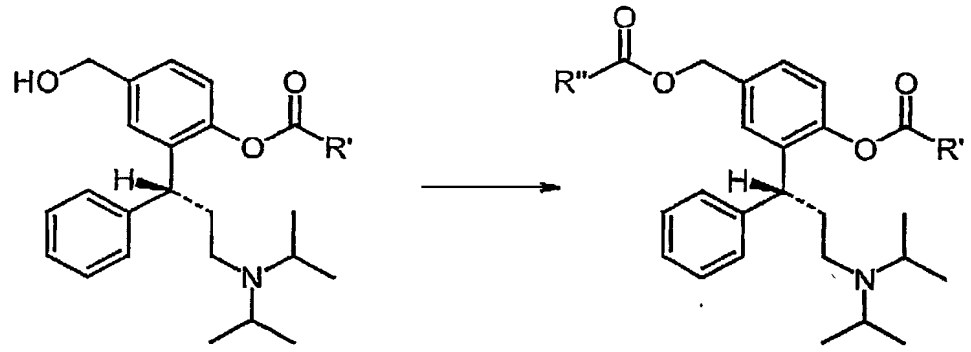
Hydrogen fumarate salt: colourless syrup, 94.4% HPLC purity.
^{13}C-NMR ($CDCl_3$): 17.89,
18.07, 18.94, 18.97, 19.07, 31.22, 33.93, 34.13, 41.78, 45.62, 53.93, 65.33, 122.93, 126.82, 127.45, 127.53, 127.91, 128.75, 134.74, 135.29, 135.42, 142.04, 148.44, 170.24, 175.71, 176.79.

R = 4-(t-$C_4H_9CO_2$)-C_6H_4

R-4-(t-butylcarbonyloxy)-benzoic acid-2-(3-diisopropylamino-1-phenyl-propyl)-4-(4-t-butylcarbonyloxymethyl-benzoic acid)-phenyl-ester hydrochloride

Colourless crystals, melting point 105-7 °C.
^{13}C-NMR (DMSO-d_6): 16.49, 16.71, 17.97, 18.06, 26.84, 31.36, 38.45, 41.70, 45.24, 53.79, 53.96, 55.09, 66.11, 122.47, 122.62, 123.59, 126.42, 126.83, 127.21, 127.70, 127.88, 128.02, 128.62, 131.17, 131.86, 134.48, 135.64, 142.52, 148.35, 154.86, 155.39, 163.80, 165.09, 176.14, 176.19.

10. Mixed diesters



R` is not equal to R``

General work specification for the manufacture of mixed diesters

Into a solution of 5.30 mmol phenolic monoester of general formula A in 40 ml dichloromethane under agitation at 0°C a solution of acid chloride (5.83 mmol) in 15 ml dichloromethane is dropped. Then triethylamine-dichloromethane (0.589g/ 5.82 mmol-15 ml) is added. After 18 hours at room temperature the thin layer chromatography shows that conversion is complete. The deposit is washed successively with respectively 50 ml water, aqueous 0.1N-hydrochloric acid, 5 ml 5% aqueous sodium-hydrogen carbonate solution, 5 ml water, dried via sodium sulphate and following filtration concentrated until dry. Then it is dried in the high-vacuum until constant weight.

The following example is manufactured using this method:

R' = $CH(CH_3)_2$

R'' = CH_3

R-(+)-isobutyrate-2-(3-diisopropylamino-1-phenyl-propyl)-4-acetoxymethyl-phenyl-ester

Colourless oil.

DC (1): 0.56

^{13}C-NMR ($CDCl_3$): 19.12, 20.65, 21.05, 34.24, 37.02, 41.79, 43.79, 48.72, 65.98, 122.75, 125.98, 126.22, 127.94, 128.39, 128.84, 133.55, 137.04, 143.84, 148.58, 170.84, 175.18.

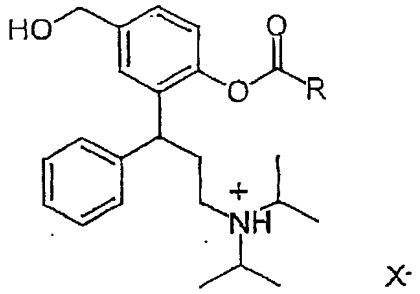
Hydrochloride: colourless crystals

^{13}C-NMR ($CDCl_3$): 16.89, 17.04, 18.31, 18.92, 20.95, 31.49, 34.07, 41,64, 46.17, 54.55, 65.49, 122.91, 126.61, 126.93, 127.48, 127.83, 128.74, 134.50, 134.88, 141.61, 148.44, 170.67, 175.63.

$[\alpha]_D^{20}$ = +14.6 (c = 1, $CHCl_3$).

CLAIMS

1. Compounds of general formula I



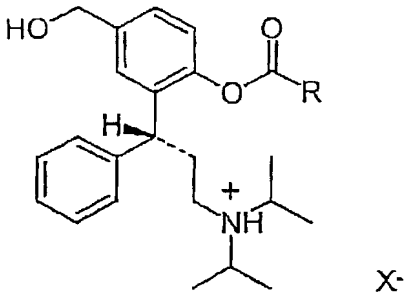
Formula I

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

2. Compounds in accordance with claim 1, characterised in that X^- in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid,

hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

3. Compounds in accordance with claims 1 and 2, characterised in that they have general formula 2.



Formula 2

in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl and X^- is the acid residue of a physiologically compatible inorganic or organic acid.

4 Compounds in accordance with claim 3, characterised in that X^- in each case is an acid ester of hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-

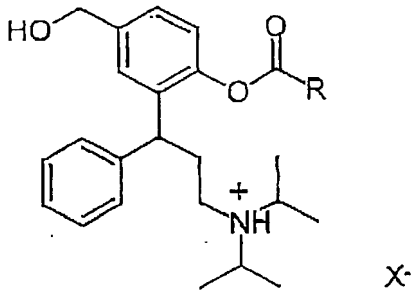
tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid.

5. Compounds in accordance with claims 3 and 4, characterised in that they are *R*-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethyl-phenylisobutyrate ester hydrogen fumarate, *R*-(+)-2-(3-(diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester-hydrochloride hydrate

6. Compounds in accordance with claims 3 and 4, characterised in that R stands for cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, 4-(1-cyclopropyl-methanoyloxy)-phenyl, 4-(1-cyclobutyl-methanoyloxy)-phenyl, 4-(1-cyclohexyl-methanoyloxy)-phenyl or 4-(2,2-dimethyl-propanoyloxy)-phenyl and X^- denotes chloride.

7. Compounds in accordance with claims 1 to 6 in the form of a bulk material.

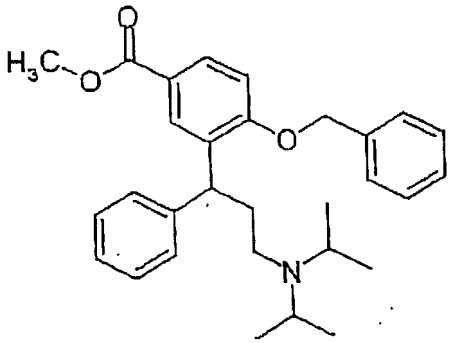
8. Method for manufacturing compounds of general formula I



Formula I

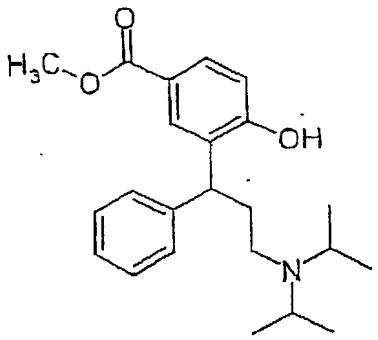
in which R denotes C_1-C_6-alkyl, C_3-C10-cycloalkyl, substituted or unsubstituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid, characterised in that

a) a compound of formula III



Formula III

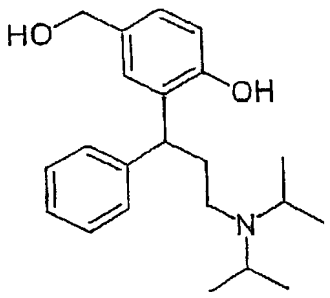
is split with a hydrogenation agent to form a compound of Formula V



Formula V

whereupon

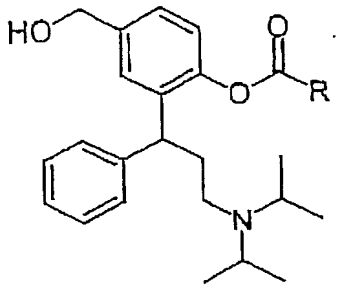
b) the compound of formula V so obtained is converted with a reducing agent, in order to give a compound of formula VI



Formula VI

which

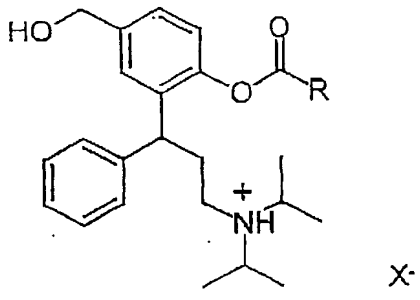
c) is converted with an acylation agent, in order to obtain a compound of formula A



Formula A

in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula I

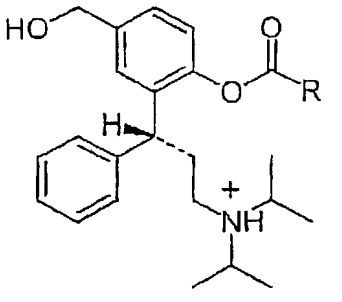


Formula I

in which R denotes C_1-C6-alkyl, C_3-C10-cycloalkyl, unsubstituted or substituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

9. Method in accordance with claim 8, characterised in that for the manufacture of the compounds of general formula I hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

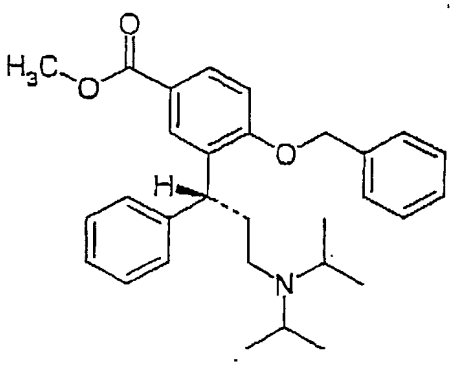
10. Method for manufacturing compounds of general formula 2



Formula 2

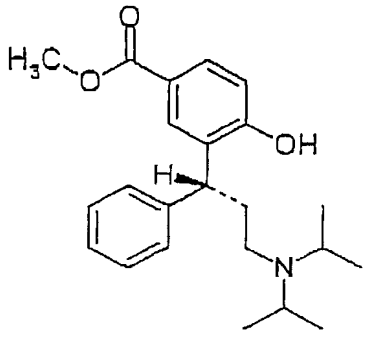
in which R denotes C_1-C_6-alkyl, C_3-C10-cycloalkyl, substituted or unsubstituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid, characterised in that

a) a compound of the formula 3



Formula 3

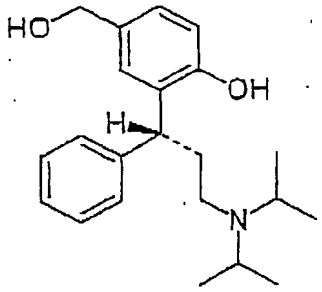
is split with a hydrogenation agent to form a compound of formula 5



Formula 5

whereupon

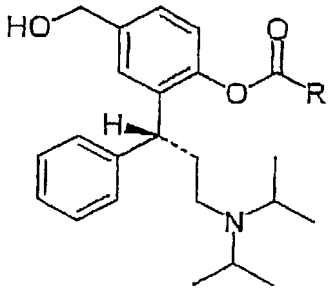
b) the compound of formula 5 so obtained is converted with a reducing agent, in order to give a compound of formula 6



Formula 6

which

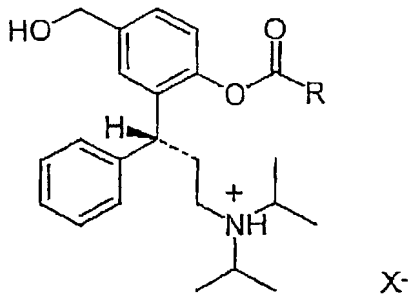
c) is converted with an acylation agent, in order to obtain a compound of formula 1



Formula 1

in which R has the significance stated above, which

d) is converted with a physiologically compatible inorganic or organic acid to form a compound of formula 2



Formula 2

in which R denotes C_1-C6-alkyl, C_3-C10-cycloalkyl, unsubstituted or substituted phenyl and X- is the acid residue of a physiologically compatible inorganic or organic acid.

11. Method in accordance with claim 10, characterised in that for the manufacture of the compounds of general formula 2 hydrochloric acid, hydrobromic acid, phosphoric acid, sulphuric acid, nitric acid, acetic acid, propionic acid, palmitic acid, stearic acid, maleic acid, fumaric acid, oxalic acid, succinic acid, DL-malic acid, L-(-)-malic acid, D-(+)-malic acid, DL-tartaric acid, L-(+)-tartaric acid, D-(-)-tartaric acid, citric acid, L-aspartic acid, L-(+)-ascorbic acid, D-(+)-glucuronic acid, 2-oxopropionic acid (pyruvic acid), furan-2-carboxylic acid (mucic acid), benzoic acid, 4-hydroxybenzoic acid, salicyclic acid, vanillic acid, 4-hydroxycinammic acid, gallic acid, hippuric acid (N-benzoyl-glycine), aceturic acid (N-aectylglycine), phloretinic acid (3-(4-

hydroxyphenyl)-propionic acid), phthalic acid, methanesulfonic acid or orotic acid are used.

12. Method in accordance with claims 8 to 11, characterised in that as the hydrogenation agent, Raney nickel/H_2 in methanol is preferably used as the solvent.

13. Method in accordance with claims 8 to 11, characterised in that for the reducing agent $NaBH_4$/EtOH, preferably $LiAlH_4$/THF, is used.

14. Method in accordance with claims 8 to 11, characterised in that for the acylation agent isobutyrylchloride and for the base triethylamine are used.

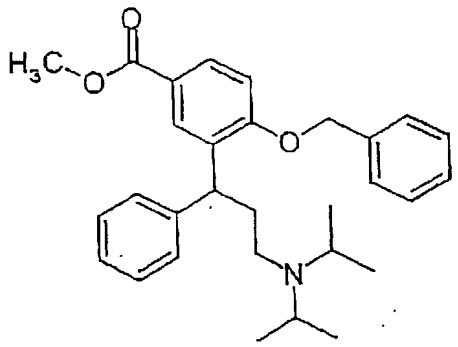
15. Method in accordance with claims 10 to 14, characterised in that a compound of general formula 6 is converted with an equivalent isobutyryl chloride in the presence of triethylamine using one of the respective solvents ethylacetate, dichloromethane, tetrahydrofurane, acetonitrile or toluene regio- and chemoselectively into *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate.

16. Method in accordance with claims 10 to 15, characterised in that *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester and fumaric acid or

hydrochloric acid are converted with the formation of the respective salt.

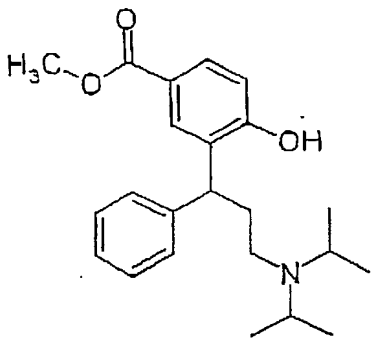
17. Method in accordance with claims 10 to 13 for the manufacture of R-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxy-methylphenylisobutyrate ester hydrochloride hydrate, characterised in that the phenolic esterification of R-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenol (6) is carried out without the addition of an external base, in that solutions of (6) are dropped into solutions of isobutyrate chloride, that contain at least 1 mole equivalent of water, in order to directly obtain a corresponding stable, hydrate-containing hydrochloride.

18. Compound of formula III



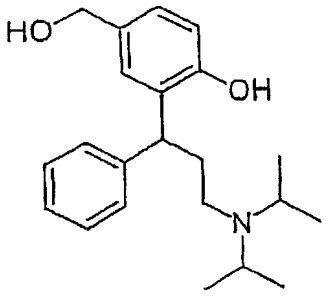
Formula III

19. Compound of formula V



Formula V

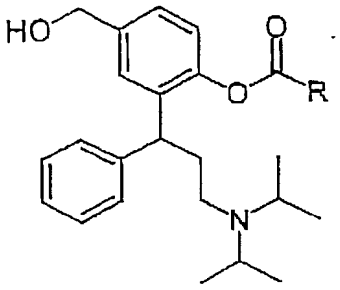
20. Compound of formula VI



Formula VI

21. Use of a compound in accordance with claims 18 to 20 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds.

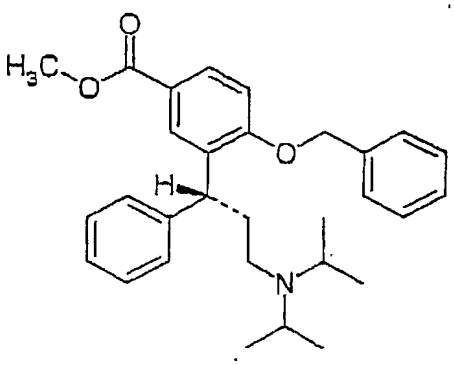
22. Use of a compound in accordance with claims 18 to 20 as an intermediate product in the manufacture of phenolic monoesters of general formula A



Formula A

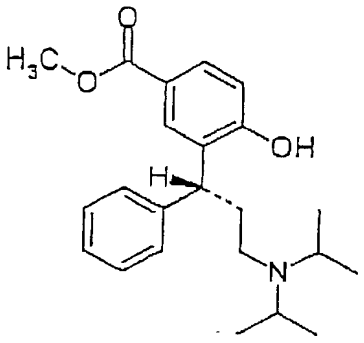
in which R denotes C_1-C_6-alkyl, C_3-C_{10}-cycloalkyl, substituted or unsubstituted phenyl.

23. Compound of formula 3



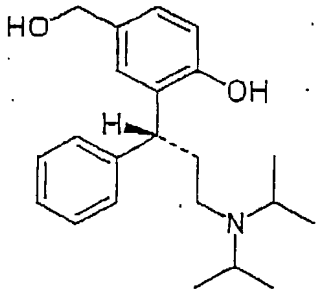
Formula 3

24. Compound of formula 5



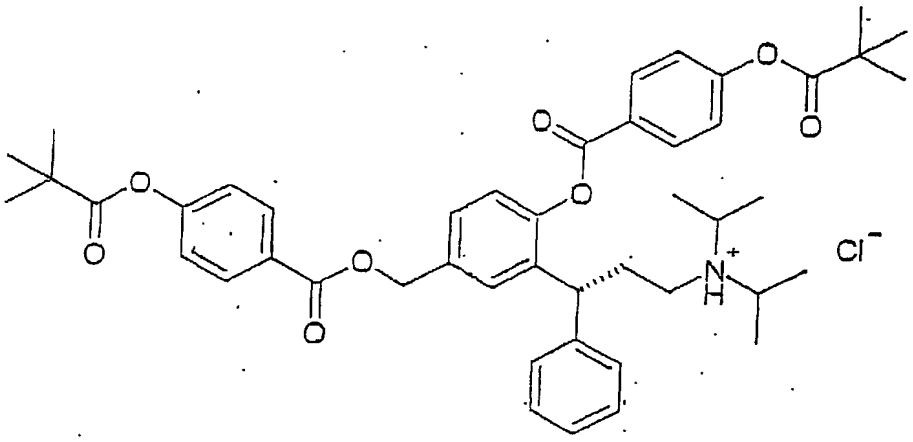
Formula 5

25. Compound of formula 6



Formula 6

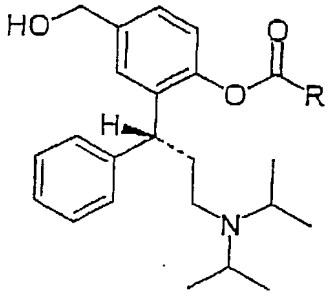
26. Compound of formula 7



Formula 7

27. Use of a compound in accordance with claims 23 to 26 as a highly pure, crystalline, stable intermediate product in the manufacture of pharmaceutically useful compounds.

28. Use of a compound in accordance with claims 23 to 26 as an intermediate product in the manufacture of phenolic monoesters of general formula 1



Formula 1

29. Use of a compound in accordance with claims 23 to 26 as an intermediate product in the manufacture of salts of phenolic monoesters of general formula 2, in which R has the same meaning as given in claim 3.

30. Use of a compound in accordance with claims 23 to 26 as an intermediate product in the manufacture of *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate and *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxymethylphenylisobutyrate ester hydrochloride hydrate.

ABSTRACT

The present invention concerns highly pure, crystalline, stable compounds of novel derivatives of 3,3-diphenylpropylamines in the form of their salts, a method for the manufacture and highly pure, stable intermediate products.

The method is in particular characterised by regio- and chemoselectivity and high yield. Salts of phenolic monoesters of 3,3-diphenylpropylamines are provided, that are particularly well-suited for use in pharmaceutical formulations. Preferred compounds are *R*-(+)-2-(3-diisopropylamino-1-phenyl-propyl)-4-hydroxymethylphenylisobutyrate ester hydrogen fumarate and *R*-(+)-2-(3-diisopropylamino-1-phenylpropyl)-4-hydroxy-methylphenylisobutyrate ester hydrochloride hydrate. Furthermore, stable, crystalline intermediate products that are essential for obtaining the abovementioned salts are provided. A preferred intermediate product is *R*-(-)-3-(3-diisopropylamino-phenyl-propyl)-4-hydroxy-benzoic acid methyl ester