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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
C07J 75/00, 3/00, 43/00
C07J 51/00, 31/00

A1

(11) International Publication Number: **WO 93/16098**

(43) International Publication Date: 19 August 1993 (19.08.93)

(21) International Application Number: PCT/US93/01071

(22) International Filing Date: 5 February 1993 (05.02.93)

(30) Priority data:
07/832,279 7 February 1992 (07.02.92) US

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(81) Designated States: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, RO, RU, SD, SE, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, SN, TD, TG).

Published
With international search report.

(54) Title: PROCESS OF PREPARING 3-ACYLANDROSTADIENES

(57) Abstract

Invented is an improved process for the preparation of substituted steroidal dienes.

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Too Short: Process of Preparing 3-Acylandrostadienes

The present invention relates to an improved process for the preparation of substituted steroidal dienes. Such compounds are described in US Patent No. 5,017,568, issued on May 21, 1991 to Holt et al., as being useful in inhibiting steroid 5-α-reductase.

Background of the Invention

Processes for the preparation of substituted steroidal diene derivatives, have previously been described. In particular the use of oxalyl bromide to convert steroidal α,β-unsaturated-3-ketones to 3-bromo-3,5-diene intermediates (in 40% yield) followed by catalytic or alkyllithium mediated carboxylation (in 15% yield when N-butyl lithium was used) to yield steroidal-3,5-diene-3-carboxylic acid derivatives is reported in US Patent No. 5,017,568.

In addition to a low overall yield, another shortcoming of this disclosure is that oxalyl bromide is a toxic, expensive liquid which is difficult to store and is not commercially available in the bulk amounts needed for an industrial process.

The use of oxalyl chloride to halogenate steroidal α,β-unsaturated ketones to chloro-steroidal dienes proceeds with only marginal results. Furthermore, the relatively low reactivity of the resultant chloro substituent poses non-trivial synthetic considerations in subsequent transformations. Thus, there is a need in the art for a safe, economical and reliable method to convert steroidal α,β-unsaturated ketones to their corresponding carboxylic acid-1,3-dienes derivatives.

SUMMARY OF THE INVENTION

This invention relates to a process for the fluorosulphonylation of multiple functional groups on the same molecule.

This invention specifically relates to a process for the simultaneous fluorosulphonylation and amidation of 3-one-4-ene-17-carboxylic acid steroidal compounds.

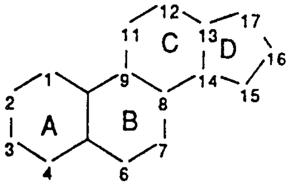
This invention specifically relates to an improved process for the preparation of N-t-butyl-androst-3,5-diene-17β-carboxamide-3-carboxylic acid.

In a further aspect of the invention there are provided novel intermediates useful in the presently invented process.

Detailed Description of the Invention

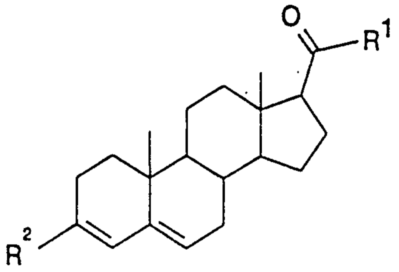
By the term "simultaneous" as used herein is meant that the transformation of the steroidal 3-one to 3-fluorosulphonyl and 17-carboxylic acid to 17-carboxamide is performed in a single reaction without the isolation of an intermediate.

As used above and throughout the remainder of the specification and claims the carbons of the steroid nucleus are numbered and the rings are lettered as follows:



Pharmaceutically acceptable salts, hydrates and solvates of Formula (I) compounds are formed where appropriate by methods well known to those of skill in the art.

The present invention provides a process for the production of a compound of formula (I)



(I)

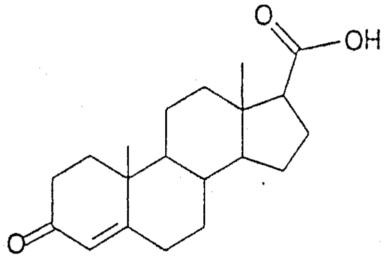
in which:

R^1 is NR^3R^4, where R^3 and R^4 are each independently selected from hydrogen, C_{1-8}alkyl, C_{3-6}cycloalkyl, phenyl; or R^3 and R^4 taken together with the nitrogen to which they are attached represent a 5-6 membered saturated ring comprising up to one other heteroatom selected from oxygen and nitrogen; and

R^2 is an acid or ester;

or a pharmaceutically acceptable salt, hydrate or solvate thereof, which comprises

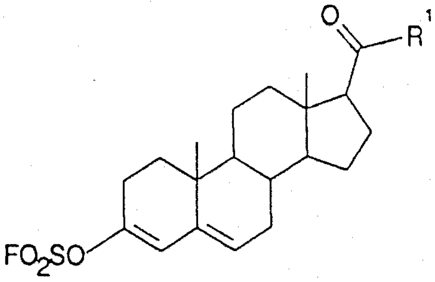
(a) reacting a compound of Formula (II)



(II)

with fluorosulfonic anhydride and a base in a solvent;

(b) quenching the reaction with excess H-R^1, where R^1 is as described above, to form a compound of Formula (III)



(III)

in which

R^1 is as defined above; and

(c) subsequently reacting said compound of formula III in a metal-catalyzed coupling reaction in the presence of coupling reagent, followed by an optional, if applicable, hydrolysis reaction to form a compound of Formula (I), and thereafter optionally forming a pharmaceutically acceptable salt, hydrate or solvate thereof.

Preferably the reaction to convert Formula II compounds to formula III is performed at a temperature from -78°C to 20°C; A particularly preferred temperature range is from -10°C to 10°C.

Preferably the reaction to convert Formula III compounds to Formula I compounds is performed at a temperature of 25°C to 100°C; a particularly preferred temperature range is from 50 to 90°C.

As such, compounds of the Formula III are particularly useful as intermediates in the preparation of Formula I compounds.

As used herein and in the claims, unless otherwise specified, C_{1-n} alkyl means a straight or branched hydrocarbon chain having 1-n carbons.

By the term "acid" as used herein and in the claims is meant any group which is capable of acting as a proton donor including but not limited to; -COOH, $-P(O)(OH)_2$, -PH(O)OH, $-SO_3H$ and $-(CH_2)_{1-3}$-COOH.

By the term "ester" as used herein and in the claims is meant a group consisting of an acid, as defined above, in which the donatable proton or protons are replaced by alkyl substituents.

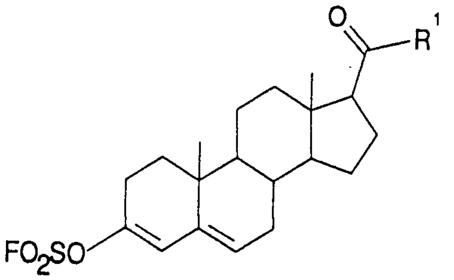
By the term "solvent" as used herein and in the claims is meant an organic solvent such as methylene chloride, ethylene chloride, chloroform, carbon tetrachloride, tetrahydrofuran (THF), ethyl ether, toluene, ethyl acetate, dimethylsufloxide, methanol or dimethylforamide.

Preferably the base utilized to prepare compounds of Formula II is triethylamine or pyridine, most preferably pyridine. Preferably the solvent utilized to prepare compounds of Formula II is methylene chloride. Preferably the catalyst utilized in said metal catalyzed coupling reaction is palladium (II) acetate. Preferred acids used to describe R^2 in Formula (I) include; -COOH, $-P(O)(OH)_2$, -PH(O)OH, $-SO_3H$, and $(CH_2)_1$-COOH. Particularly preferred among the above acids is -COOH.

By the term "metal-catalyzed coupling reaction" as used herein and in the claims is meant that the prepared fluorosulfonated compound is reacted in a suitable organic solvent; preferably a dimethylsulfoxide-alkanol(C_1-C_6) solution (when an ester is desired) or toluene, dimethylformamide, THF or C_4-C_6OH (when an acid is desired) with a base, preferably a tertiary amine base such as triethylamine, pyridine or tributylamine or aqueous KOH or aqueous NaOH; a phosphine such as bis(diphenylphosphino)alkane, preferably 1,3 bis(diphenylphosphino)propane or tri-o-tolylphosphine, and a metal catalyst, preferably a palladium catalyst such as palladium (II) acetate, palladium (II) chloride and bis(triphenylphosphine) palladium II acetate, thereby forming a metalated complex with subsequent addition of a coupling reagent.

By the term "coupling reagent" as used herein and in the claims is meant a compound which is capable of inserting into said metalated complex with subsequent elimination to yield the corresponding ester or acid. Preferred coupling reagents, which when added to the metal-catalyzed coupling reaction, as described herein, yield preferred acid and ester groups, as disclosed herein, are carbon monoxide (to yield $-COOC_{1-6}$), formic acid (to yield -COOH), ethyltributylstannyl acetate (to yield $-CH_2COOH$), dimethyl phosphite (to yield $-P(O)(OH)_2$) and hypophosphorous acid crystals (to yield -PH(O)OH).

In utilizing the presently invented process to prepare the preferred compounds of Formula (I), novel intermediates of the following Formula (IV) are synthesized

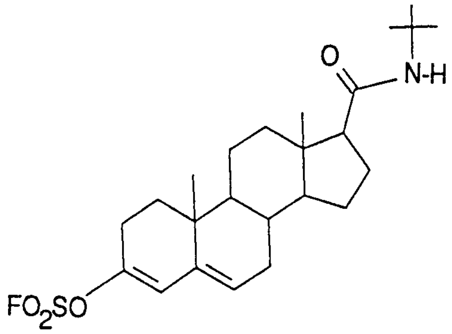


(IV)

in which

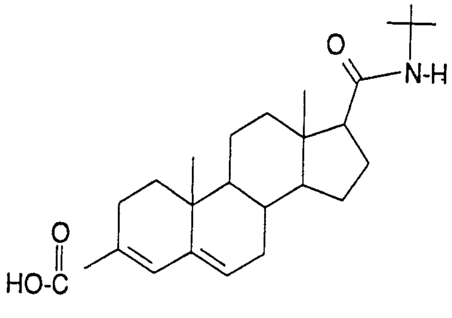
R^1 is $CONR^3R^4$, where R_3 and R_4 are each independently selected from hydrogen, C_{1-8}alkyl, C_{3-6}cycloalkyl, phenyl; or R^3 and R^4 taken together with the nitrogen to which they are attached represent a 5-6 membered saturated ring comprising up to one other heteroatom selected from oxygen and nitrogen.

Preferably, therefore the process of the present invention is particularly useful for preparing a compound of Structure IIA



(IIA)

and converting the same in one or two steps into the following compound of structure (IA)



(IA)

or a pharmaceutically acceptable salt, hydrate or solvate thereof.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

1,3-Bis(diphenylphosphino)propane, bis(triphenylphosphine)palladium acetate, and palladium acetate, are commonly available. Androst-4-en-3-one-17β-carboxylic acid is available from Berlichem, Inc. (Wayne, NJ).

Fluorosufonic anhydride was prepared as described by S. Kongpricha, et. al., *Inorg. Syn.* 1968, XI, 151.

Example 1

N-t-butyl-androst-3,5-diene-17β-carboxamide-3-carboxylic acid

(i). N-t-butyl-androst-3,5-diene-3-fluorosulphonyl-17β-carboxamide

A stirred mixture of androst-4-en-3-one-17β-carboxylic acid (1 molar equivalent) and pyridine (3 molar equivalents) in 1000 mL of methylene chloride is cooled to 0-5°C, and is treated with fluorosulfonic anhydride (2.5 molar equivalents) while maintaining the temperature between 0-10°C. After stirring for one hour, the reaction mixture is quenched into a solution of tert-butylamine (10 molar equivalents) in methylene chloride while maintaining the temperature between 0-10°C. The mixture is stirred for 30 minutes. About 100 mL of water is added. The organic phase is separated and reduced to about half its volume by vacuum distillation. The solution is restored to its original volume with acetone. This concentration/fill procedure is repeated twice more. The resulting acetone solution (about 300 mL) is warmed to about 50°C and is treated with about 100 mL of water to precipitate the product. The suspension is cooled, and N-t-butyl-androst-3,5-diene-3-fluorosulphonyl-17β-carboxamide is isolated by filtration and dried.

(ii) Methyl 17ß-(N-tert-butylcarboxamide)-androst-3,5-diene-3-carboxylate

A vessel is charged with dimethylsulfoxide (1350 mL), methanol (75 mL, 5.4 molar equivalents), N-t-butyl-androst-3,5-diene-3-fluorosulphonyl-17ß-carboxamide (150 g, 1 molar equivalent), triethylamine (76.3 g, 2.2 molar equivalents), and 1,3-bis(diphenylphosphino)propane (1.4 g, 0.01 molar equivalent). The mixture is stirred until a solution is obtained. Palladium acetate (0.768 g, 0.01 molar equivalent) is added and the flask is filled and evacuated with carbon monoxide three times. The vessel is pressurized with 7 psi carbon monoxide and the reaction is stirred rapidly. The reaction solution is heated to 75°C. The carbon monoxide uptake is finished in about 1.5 hours. The reaction is cooled to 15°C and stirred for 2 hours. The solid product is isolated by suction filtration, and the mother liquors are used to rinse out the inside of the reactor. The solid product is thoroughly washed with water (1.5 L) and dried under vacuum at 95°C to afford pure methyl 17ß-(N-tert-butylcarboxamide)-androst-3,5-diene-3-carboxylate.

(iii). N-t-butyl-androst-3,5-diene-17ß-carboxamide-3-carboxylic acid

A mixture of methanol (80 mL), water (80 mL), methyl 17ß-(N-tert-butylcarboxamide)-androst-3,5-diene-3-carboxylate (15.9 g, 1 molar equivalents) and sodium hydroxide (4.80 g, 3 molar equivalent), is heated to reflux for 8-12 hours. The hot reaction solution is filtered through celite and the filter pad is washed with 60°C water (80 mL). The filtrate is diluted with water (80 mL). The methanol is removed by distillation to a head temperature of 100°C. The mixture is cooled to 60°C and is quenched with vigorous stirring into 1.5 N hydrochloric acid (160 mL). The resulting white suspension is stirred for 15 minutes. The slurry is cooled to 0-5°C and stirred for 1 hour. The product is isolated by filtration, washed with deionized water, and dried under vacuum at 100°C to afford N-t-butyl-androst-3,5-diene-17ß-carboxamide-3-carboxylic acid.

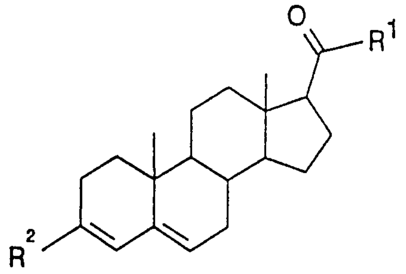
Example 2

N-t-butyl-androst-3,5-diene-17ß-carboxamide-3-carboxylic acid

A vessel is charged with 5 volumes of dimethylformamide, N-t-butyl-androst-3,5-diene-3-fluorosulphonyl-17ß-carboxamide (1 molar equivalent, prepared as described in Example 1(i)), tri-n-butylamine (4.5 molar equivalents), formic acid (2 molar equivalents) and bis(triphenylphosphine)palladium acetate (0.02 molar equivalents). The flask is evacuated and filled with carbon monoxide three times. The vessel is pressurized with 7 psi carbon monoxide and the reaction is stirred rapidly. The reaction solution is heated to 75°C until the uptake of carbon monoxide is complete. The reaction is cooled to room temperature. Ethyl acetate and water are added, and the organic layer is separated. The organic phase is washed with water and dried over magnesium sulfate. The organic phase is concentrated under vacuum to yield N-t-butyl-androst-3,5-diene-17ß-carboxamide-3-carboxylic acid.

What is claimed is:

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



(I)

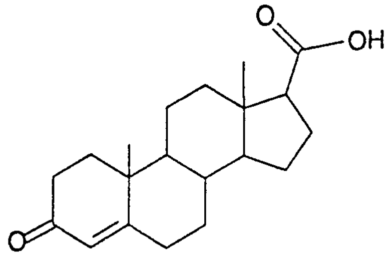
in which:

R^1 is NR^3R^4, where R^3 and R^4 are each independently selected from hydrogen, C_{1-8} alkyl, C_{3-6} cycloalkyl, phenyl; or R^3 and R^4 taken together with the nitrogen to which they are attached represent a 5-6 membered saturated ring comprising up to one other heteroatom selected from oxygen and nitrogen; and

R^2 is an acid or ester;

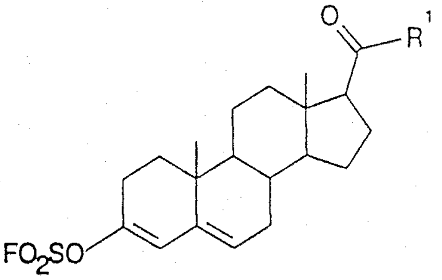
or a pharmaceutically acceptable salt, hydrate or solvate thereof, which comprises

(a) reacting a compound of Formula (II)



(II)

with fluorosulfonic anhydride and a base in a solvent then quenching with excess H-R^1, where R^1 is as defined above, to form a compound of Formula (III)



(III)

in which

R^1 is as defined above and

(b) subsequently reacting said compound of Formula III in a metal-catalyzed coupling reaction in the presence of a coupling reagent, followed by an optional, if applicable, hydrolysis reaction to form a compound of Formula (I) and thereafter optionally forming a pharmaceutically acceptable salt, hydrate or solvate.

2. A process according to claim 1 in which R^1 is $-N(H)C(CH_3)_3$.

3. A process according to claim 1 in which said base is selected from pyridine or triethylamine.

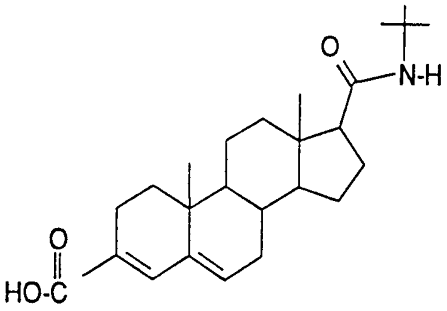
4. A process according to claim 3 in which the base is pyridine.

5. A process according to claim 1 in which the metal-catalyzed coupling reaction comprises 1,3-bis(diphenylphosphino)propane.

6. A process according to claim 1 in which the metal-catalyzed coupling reaction comprises palladium acetate.

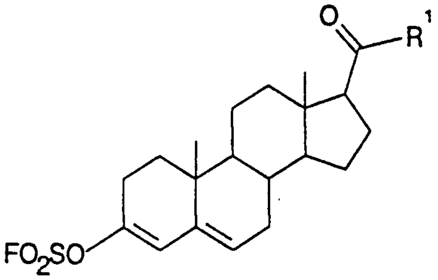
7. A process according to claim 1 in which the coupling reagent is formic acid.

8. A process according to claim 3 in which the compound prepared is



or a pharmaceutically acceptable salt, hydrate or solvate thereof.

9. A compound of the structure



in which;

R^1 is NR^3R^4, where R^3 and R^4 are each independently selected from hydrogen, C_{1-8} alkyl, C_{3-6} cycloalkyl, phenyl; or R^3 and R^4 taken together with the nitrogen to which they are attached represent a 5-6 membered saturated ring comprising up to one other heteroatom selected from oxygen and nitrogen.

INTERNATIONAL SEARCH REPORT

PCT/US93/01071

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :C07J 75/00, 3/00,43/00,51/00,31/00
US CL :552/506,524,610
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)

U.S. :

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 practicable, search terms used)

CAS Search-Structure Search

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	US,A, 4,946,834 (HOLT, ET AL) 07 AUGUST 1990 See schemes 1.1, V,IX, and example 1	1-6 9
X Y	Holt, et al., J. Med. Chem. 1990, 33 943-950 "Inhibition of steroidal 5 Reductase by Unsaturated 3-Carboxylsteroids" See p. 946-947	1-6 and 8 9
X Y	US,A, 5,032,586 (METCALF ET AL) 16 JULY 1991 See example 1	1-6 and 8 9

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

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Date of the actual completion of the international search 02 APRIL 1993	Date of mailing of the international search report 03 JUN 1993
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer EDWARD C. WARD
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US93/01071

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Roth et al, J. Org. Chem. 1991 56,3493-3496 "Palladium Cross-Coupling Reactions Aryl Fluorosulfonates: An Alternative to Triflate Chemistry"	1-6 and 8-9
A	Scott, et al, J. Am Chem. Soc. 1984 106 4630-4632 "Palladium-Catalyzed Coupling of Vinyl Triflates with Organostannes=	1-9