

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION

International Office

INTERNATIONAL APPLICATION PUBLISHED ACCORDING TO THE PATENT
COOPERATION TREATY (PCT)

- (51) International patent classification⁶: C07J 53/00 A1
- (11) International publication number: WO 98/06738
- (43) International publication date: February 19, 1998 (2/19/98)
- (21) International file number: PCT/EP97/04342
- (22) International application date: August 11, 1997 (8/11/97)
- (30) Priority data: 196 33 685.6 August 12, 1996 (8/12/96) DE
- (71) Applicant (for all designated countries except US):
SCHERING AKTIENGESELLSCHAFT [DE/DE]; Patents, Müllerstrasse
178, P. O. Box 65 03 11, D-13342 Berlin (DE).
- (72) Inventors; and
- (75) Inventors/applicants (only for US):
MOHR, Jörg-Thorsten [DE/DE]; Zwinglistrasse 4, D-10555
Berlin (DE). NICKISCH, Klaus [DE/DE]; Zescher Strasse 14,
D-12307 Berlin (DE).
- (74) Joint Representative: SCHERING AKTIENGESELLSCHAFT, Patents,
Müllerstrasse 178, P. O. Box 65 03 11, D-13342 Berlin (DE).
- (81) Designated countries: AL, AM, AT, AU, AZ, BB, BG, BR, BY,
CA, CH, CN, CZ, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE,
KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW,
MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR,
TT, UA, UG, US, UZ, VN, ARIPO Patent (GH, KE, LS, MW, SD,
SZ, UG, ZU), Eurasian Patent (AM, AZ, BY, KG, KZ, MD, RU,
TJ, TM), European Patent (AT, BE, CH, DE, DK, ES, FI, FR,
GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI Patent (BF, BJ,
CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

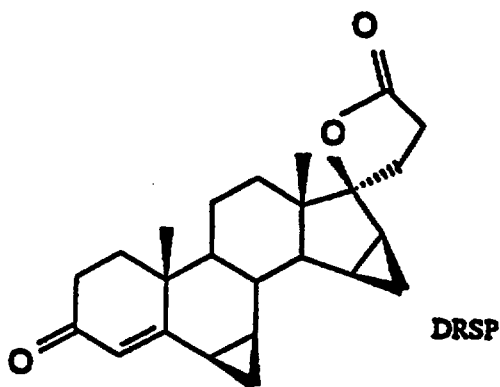
Published:

With international search report.

(54) Title: PROCESS FOR THE PRODUCTION OF DROSPIRENONE (6 β ,7 β ; 15 β ,16 β -DIMETHYLENE-3-OXO-17 α -PREGN-4-ENE-21,17-CARBOLACTONE, DRSP) AND 7 α -(3-HYDROXY-1-PROPYL)-6 β ,7 β ; 15 β ,16 β -DIMETHYLENE-5 β -ANDROSTANE-3 β ,5,17 β -TRIOL (ZK [CENTRAL CATALOG] 92836) AND 6 β ,7 β ; 15 β ,16 β -DIMETHYLENE

(57) Abstract

Process for the production of drospirenone (6 β ,7 β ; 15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone, DRSP) (1) and 7 α -(3-hydroxy-1-propyl)-6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -androstane-3 β ,5,17 β -triol (ZK 92836) and 6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -hydroxy-3-oxo-17 α -androstane-21,17-carbolactone (ZK 90965) as intermediate products of the process.



(1)

FOR INFORMATION ONLY

Codes used for identifying PCT member countries on the head sheets of the publications of international applications according to the PCT.

AL	Albania
AM	Armenia
AT	Austria
AU	Australia
AZ	Azerbaijan
BA	Bosnia and Herzegovina
BB	Barbados
BE	Belgium
BF	Burkina Faso
BG	Bulgaria
BJ	Benin
BR	Brazil
BY	Belarus
CA	Canada
CF	Central African Republic
CG	Congo
CH	Switzerland
CI	Ivory Coast
CM	Cameroon
CN	China
CU	Cuba
CZ	The Czech Republic
DE	Germany
DK	Denmark
EE	Estonia
ES	Spain
FI	Finland
FR	France
GA	Gabon
GB	United Kingdom
GE	Georgia
GH	Ghana
GN	Guinea
GR	Greenland
HU	Hungary
IE	Ireland
IL	Israel
IS	Iceland
IT	Italy
JP	Japan
KE	Kenya
KG	Kyrgyzstan

KP	Democratic People's Republic of Korea
KR	Republic of Korea
KZ	Kazakhstan
LC	St. Lucia
LI	Liechtenstein
LK	Sri Lanka
LR	Liberia
LS	Lesotho
LT	Lithuania
LU	Luxembourg
LV	Latvia
MC	Monaco
MD	Republic of Moldova
MG	Madagascar
MK	the former Yugoslavian Republic of Macedonia
ML	Mali
MN	Mongolia
MR	Mauritania
MW	Malawi
MX	Mexico
NE	Niger
NL	The Netherlands
NO	Norway
NZ	New Zealand
PL	Poland
PT	Portugal
RO	Romania
RU	Russian Federation
SD	Sudan
SE	Sweden
SG	Singapore
SI	Slovenia
SK	Slovakian Republic
SN	Senegal
SZ	Swaziland
TD	Chad
TG	Togo
TJ	Tajikistan
TM	Turkmenistan
TR	Turkey
TT	Trinidad and Tobago
UA	The Ukraine
UG	Uganda
US	United States of America
UZ	Uzbekistan
VN	Vietnam
YU	Yugoslavia
ZW	Zimbabwe

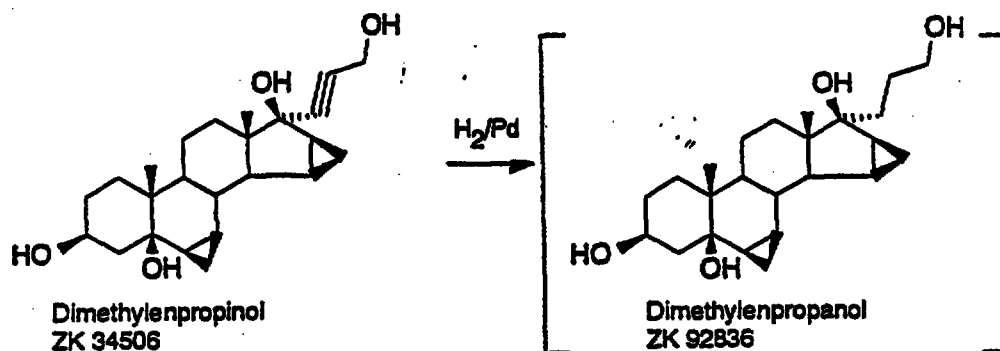
Process for the Production of Drospirenone (6 β ,7 β ; 15 β ,16 β -Dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone, DRSP)
and

7 α -(3-Hydroxy-1-propyl)-6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -androstane-3 β ,5,17 β -triol (ZK 92836) and 6 β ,7 β ; 15 β ,16 β -Dimethylene-5 β -hydroxy-3-oxo-17 α -androstane-21,17-carbolactone (90965)

as Intermediate Products of the Process.

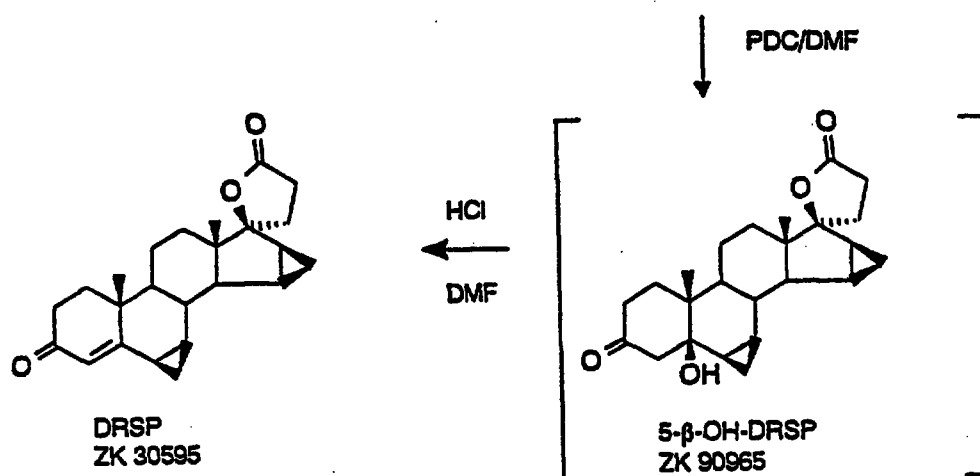
The invention relates to a process for the production of drospirenone (6 β ,7 β ; 15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone, DRSP) and 7 α -(3-hydroxy-1-propyl)-6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -androstane-3 β ,5,17 β -triol (ZK 92836) and 6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -hydroxy-3-oxo-17 α -androstane-21,17-carbolactone (ZK 90965) as intermediate products of the process.

Drospirenone (6 β ,7 β ; 15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone, DRSP, INN) has been known for some time as a steroidal active ingredient (DE 26 52 761 C2 and DE 30 22 337 A1), and the production of the last 4 steps is carried out in a single-pot reaction; in which after dimethylene propinol ZK 34506 is hydrogenated, none of the intermediate stages dimethylene propanol and 5- β -OH-DRSP that are passed through are isolated (see diagram below).



Dimethylene propinol
ZK 34506

Dimethylene propanol
ZK 92836



DRSP
ZK 30595

5- β -OH-DRSP
ZK 90965

The dimethylene propinol ZK 34506 is hydrogenated in tetrahydrofuran with hydrogen on palladium-carbon into dimethylene propanol ZK 92836. The hydrogenating solution that is thus obtained, which contains propanol ZK 92836 as the main product and varying proportions of lactol, is reacted without

isolation and intermediate working-up to drospirenone ZK 30595 (DRSP).

For this purpose, a change of solvent from tetrahydrofuran to dimethylformamide first takes place and then the propanol is oxidized at 40°C with an excess of 3.7 equivalents of pyridinium dichromate (PDC) to a mixture of DRSP and 5-β-OH-DRSP. The 5-β-OH group in the oxidation product is labile compared to acids, Lewis acids and basic conditions at elevated temperatures, since in all cases, a more thermodynamically stable product is obtained with the formation of the Δ-4,5-unsaturated ketone in the drospirenone. The elimination of the β-OH group in the 5-β-OH-DRSP results in more thermodynamically stable drospirenone, and it was not possible to suppress it.

The mixture generally contains differing proportions of the two components, whereby 5-β-OH-DRSP is generally present as a main component at a ratio of 2-3:1. In the last stage of the single-pot sequence, the two-component mixture is converted by adding semi-concentrated hydrochloric acid into the DRSP, crude.

In the table below, the last four operating preparations are summarized.

Preparation	Yield, crude (%)	Purity (100% Method)
537201	57.2	98.9
202	63.7	99.09
203	46.5	99.18
204	58.3	98.81
Total	Mean Yield: 56.4	Mean Purity: 98.9

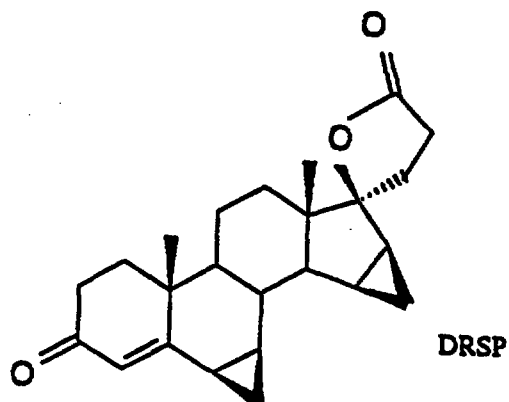
By the means of all operational preparations, starting from dimethylene propinol, a theoretical yield of 56% DRSP, crude at an HPLC purity of 98.9%, is achieved.

The object of the invention is the provision of a new production process for drospirenone, which is more selective and simpler in execution than that from the prior art and, in addition, is ecological (savings of a chromium trioxide oxidation).

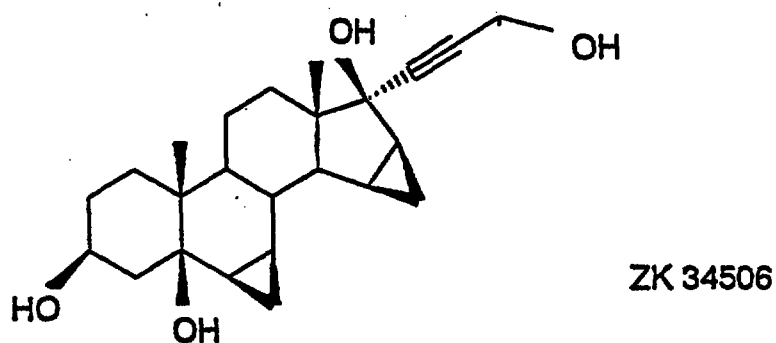
This object is achieved according to the teaching of the claims.

The invention contains a process for the production of drospirenone (6 β ,7 β ; 15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-

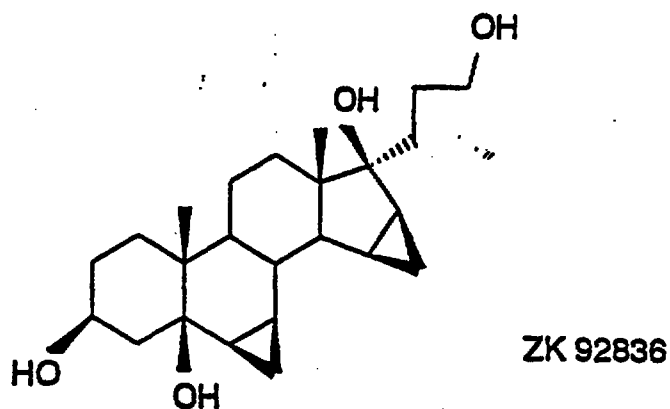
21,17-carbolactone, DRSP)



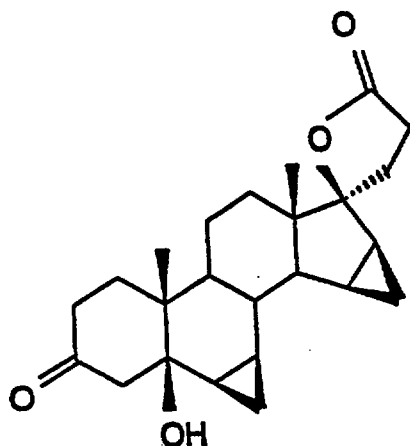
by catalytic hydrogenation of 17 α -(3-hydroxy-1-propynyl)-6 β ,7 β ;
15 β ,16 β -dimethylene-5-androstane-3 β ,5,17 β -triol (ZK 34506)



into 7 α -(3-hydroxy-1-propyl)-6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -
androstane-3 β ,5,17 β -triol (ZK 92836)



then oxidation with use of commercially available ruthenium salts, such as RuCl_3 , RuO_2 , KRuO_4 , K_2RuO_4 , but preferably in the presence of catalytic amounts of RuCl_3 (1 mol%) and conventional, simple oxidizing agents such as 'butyl hydroperoxide, N-methylmorpholine-N-oxide, $\text{M}_2\text{S}_2\text{O}_8$ ($\text{M} = \text{Na}, \text{K}$), MXO_y ($\text{M} = \text{Li}, \text{Na}, \text{K}$; $\text{X} = \text{B}, \text{Cl}, \text{Br}$, $1: y = 1-4$), but preferably 1-3 equivalents of NaBrO_3 , in solvents such as acetonitrile, chloroform, methylene chloride, carbon tetrachloride, water, tetrahydrofuran, tert-butanol, ethyl acetate or combinations thereof, but preferably in an acetonitrile-water mixture in the composition of acetonitrile:water = 1:1, in 6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -hydroxy-3-oxo-17 α -androstane-21,17-carbolactone (ZK 90965)



ZK 90965

and subsequent dehydration.

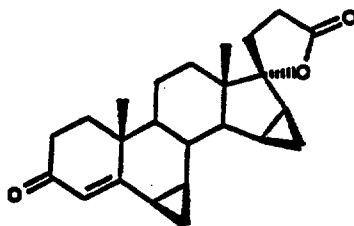
As a key reaction, the invention contains the ruthenium-catalyzed oxidation of dimethylene propanol ZK 92836 to 5- β -OH-DRSP ZK 90965 and the subsequent elimination of water to drospirenone ZK 30595 in a two-stage process.

Analogously to the known process from the prior art, in the process according to the invention, dimethylene propinol ZK 34506 is hydrogenated with hydrogen on palladium-carbon into tetrahydrofuran. The hydrogenating solution is then subjected to a change of solvent, from tetrahydrofuran to acetonitrile. The acetonitrile solution is oxidized with a catalytic amount of ruthenium trichloride (1 mol%) and 3 equivalents of sodium bromate at 40°-60°C, specifically to 5-β-OH-DRSP. Despite the significant lability of 5-β-OH-DRSP compared to acids, Lewis acids, such as, for example, chromium compounds in old operating processes, strong bases or high temperatures, which in all cases can be attributed to the high driving force to form the more thermodynamically stable Δ-4,5-unsaturated ketone, the selective synthesis of 5-β-OH-DRSP can be accomplished under the selected reaction conditions without a formation of drospirenone being observed. The 5-β-OH-DRSP can be isolated from the reaction solution by a precipitation of water that is simple to implement (operationally).

The yields are in the range of 68% to 75% via the two stages: hydrogenation and then oxidation.

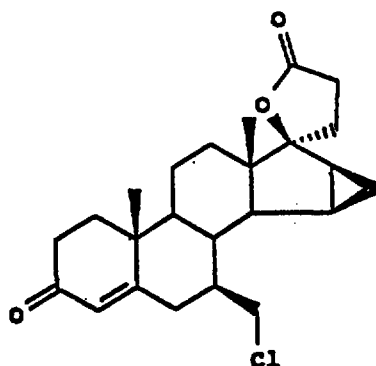
From some tests, it is known that in the case of acidic action, drospirenone can be decomposed with acidic action via two reaction routes. For one thing, under acidic conditions, the

drospirenone is easily converted into epimeric isolactone ZK 35096.



ZK 35096

The second by-product is produced by an HCl attack on the 6,7-methylene group, which results in ring opening product ZK 95673.



ZK 95673

Both by-products are pushed back under the reaction conditions of the new process to the extent that they can be observed only on an order of magnitude of $< 0.2\%$.

In the elimination, a yield of 96% of theory is achieved. The total yield of the new process thus lies in the range of 65% to 72% of theory.

Another very basic advantage of the process according to the invention compared to the prior art lies in the range of ecology. It has been possible to replace the previously used toxic chromium compounds, which so far have been used in the form of pyridinium dichromate salts for oxidation and must subsequently be disposed of in the form of their solutions, by catalytic amounts of a metal. In addition, it is possible to recycle the used acetonitrile-water mixture by azeotropic distillation, so that also no danger to the environment is likely.

The invention also contains the intermediate products 7 α -(3-hydroxy-1-propyl)-6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -androstane-3 β ,5,17 β -triol (ZK 92836) and 6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -hydroxy-3-oxo-17 α -androstane-21,17-carbolactone (90965).

WO 98/06738

PCT/EP97/04342

Examples:

6 β ,7 β ; 15 β ,16 β -Dimethylene-5 β -hydroxy-3-oxo-17 α -androstande-21,17-carbolactone

50 g of 17 α -(3-hydroxy-1-propynyl)-6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -androstande-3 β ,5,17 β -triol is hydrogenated into 1000 ml of THF in the presence of 10 g of palladium on carbon (10%) and 3 ml of pyridine until 2 equivalents of hydrogen are taken up. Then, the catalyst is filtered off, and the solution is evaporated to the dry state, whereby 52.7 g of 7 α -(3-hydroxy-1-propyl)-6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -androstande-3 β ,5,17 β -triol is obtained, which is further reacted without purification.

50.2 g of 7 α -(3-hydroxy-1-propyl)-6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -androstande-3 β ,5,17 β -triol is suspended in 250 ml of acetonitrile and heated to 45°C. 0.52 g of ruthenium trichloride, dissolved in 10 ml of water, and 62.46 g of sodium bromate, dissolved in 250 ml of water, are added in drops to the above. It is stirred for 2 more hours at 50°C, and the solution is then quenched by adding 1000 ml of water. 200 ml of ethyl acetate is added, the phases are separated and then the aqueous phase is extracted with 600 ml of ethyl acetate. The combined organic phases are dried on sodium sulfate and then evaporated to the dry state. In this case, 43.44 g of 6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -hydroxy-3-oxo-17 α -androstande-21,17-carbolactone is obtained as crude product. 35.7 g of 6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -hydroxy-3-oxo-17 α -androstande-21,17-carbolactone with a melting

point of 216°-218°C is obtained by recrystallization from acetone-isoether. The rotation is approximately -65.6°C (sodium line, $c = 1.02$ in CHCl_3).

6 β ,7 β ; 15 β ,16 β -Dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone

28 g of 6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -hydroxy-3-oxo-17 α -androstane-21,17-carbolactone is suspended in 280 ml of THF and then mixed with 10 mol% of 1.5 g of p-toluenesulfonic acid. After 30 minutes, 125 ml of saturated NaCl solution and 8.2 ml of 1N NaOH solution are added. After phase separation, the organic phase is dried on sodium sulfate and evaporated to the dry state, whereby 25.67 g of 6 β ,7 β ; 15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone is obtained as crude product, whose purity is approximately 93% according to HPLC determination.

Further purification can be done by chromatography.

The melting point of the chromatographed substance is approximately 197.5°-200°C.

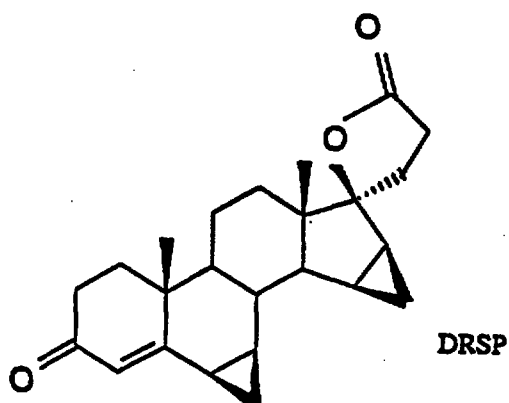


WO 98/06738

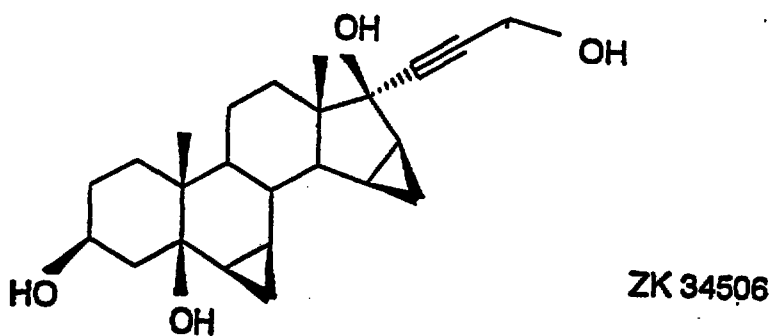
PCT/EP97/04342

Claims

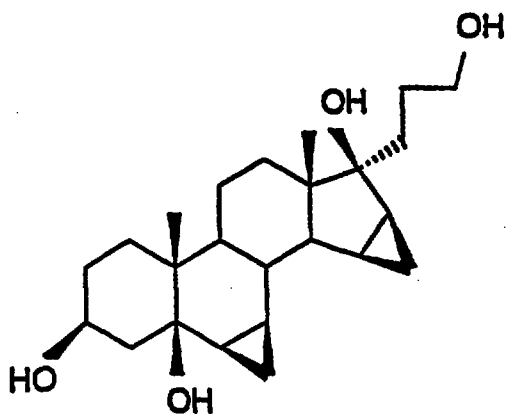
1. Process for the production of drospirenone (6 β ,7 β ; 15 β ,16 β -dimethylene-3-oxo-17 α -pregn-4-ene-21,17-carbolactone, DRSP)



by catalytic hydrogenation of 17 α -(3-hydroxy-1-propynyl)-6 β ,7 β ; 15 β ,16 β -dimethylene-5-androstane-3 β ,5,17 β -triol (ZK 34506)

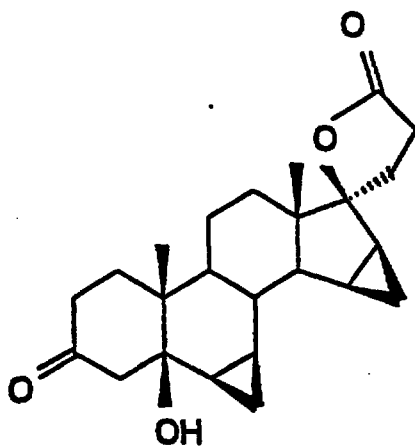


into 7 α -(3-hydroxy-1-propyl)-6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -androstane-3 β ,5,17 β -triol (ZK 92836),



ZK 92836

oxidation in the presence of a ruthenium salt into 6 β ,7 β ;
15 β ,16 β -dimethylene-5 α -hydroxy-3-oxo-17 α -androstane-21,17-
carbolactone (ZK 90965)

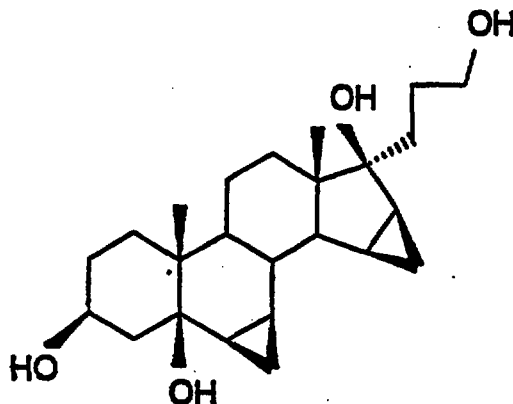


ZK 90965

and subsequent dehydration.

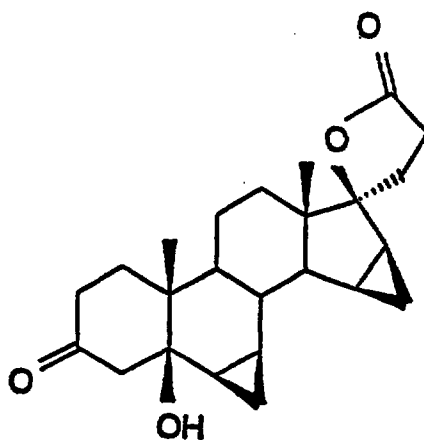


2. 7 α -(3-Hydroxy-1-propyl)-6 β ,7 β ; 15 β ,16 β -dimethylene-5 β -androsterane-3 β ,5,17 β -triol (ZK 92836)



ZK 92836

3. 6 β ,7 β ; 15 β ,16 β -Dimethylene-5 β -hydroxy-3-oxo-17 α -androsterane-21,17-carbolactone (ZK 90965)



ZK 90965