

Method for producing (+)-estrone derivatives

5 The present invention relates to a method for producing (+)-estrone derivatives useful for oral contraceptives by using dicyclopentadiene derivatives as starting materials, and to intermediates which are used for the production of (+)-estrone derivatives.

10

 (+)-Estrone is a compound useful for oral contraceptives, and it has been known from a long time to obtain the compound by methods in which natural materials are used (U.S. Patent Nos. 1967350 (1934) and 135992 (1962)).

15 However, the efficiency and yields of the methods are too inferior to those of synthetic methods to compare therewith.

 Synthetic methods for (+)-estrone whose configuration is a natural type have been developed. Posner et al. (J. Am. Chem. Soc., 108 1239(1986) disclosed that a compound
20 having an AB ring skeleton and a compound having a D ring skeleton which is asymmetrically derived are reacted by an asymmetric Michael addition reaction, and a C ring skeleton is formed by an intramolecular Diels-Alder reaction to construct an estron skeleton having a diastereoselectivity of 91-94%. However, the total yield is
25 low, 6.3%, and the process has inefficiently nine steps.

 Moreover, Taber et al. (J. Org. Chem. 52 28(1987)) constructed a β -ketoester having a D ring skeleton by using a camphor derivative as a chiral source, combined
30 the compound with a benzocyclobutene derivative, and constructed a BC ring skeleton by internal cyclization reaction in one step to synthesize (+)-estrone having an optical purity of 91%ee. However, the process has many reaction steps. To construct the β -ketoester, it needs
35 five steps. To synthesize the benzocyclobutene deriva-

tive, it needs three steps. To combine the both compounds and to obtain the objective skeleton, it needs three steps. The yield of the ring formation is low, 41%, and the total yield from the β -ketoester precursor is 9.8%.

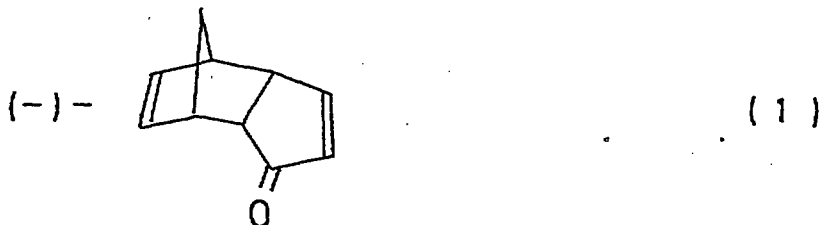
5 The stereoselectivity of the (+)-estrone is comparatively good, but the effectivity of the process is no good.

Before the present invention, (+)-estrone was much in demand, but it was not provided well.

10 As described above, the inventors of the present invention have earnestly studied to attain an object for efficiently obtaining the (+)-estrone derivatives having high optical purities, and they have found that the (+)-estrone is efficiently obtained by using dicyclopentadiene derivative as a starting material.

15 The present invention is a method for producing (+)-estrone derivatives, characterized in that it comprises starting from (-)-tricyclo [5.2.1.0^{2.6}] deca-4,8-diene-3-one (1) represented by the formula:

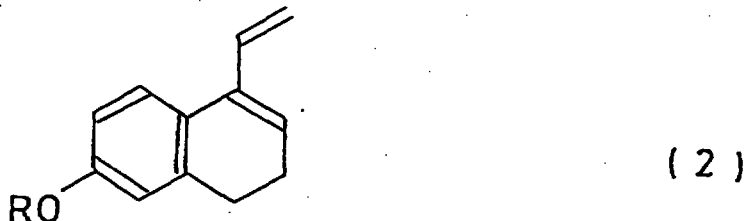
20



25

reacting the compound (1) with 4-vinyl-7-alkoxy-1,2-dihydronaphthalene (2) represented by the formula:

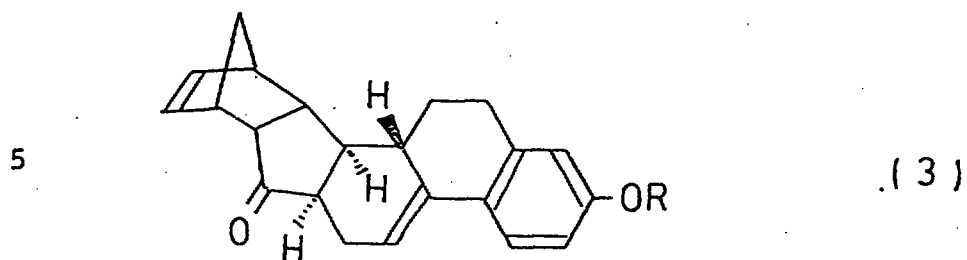
30



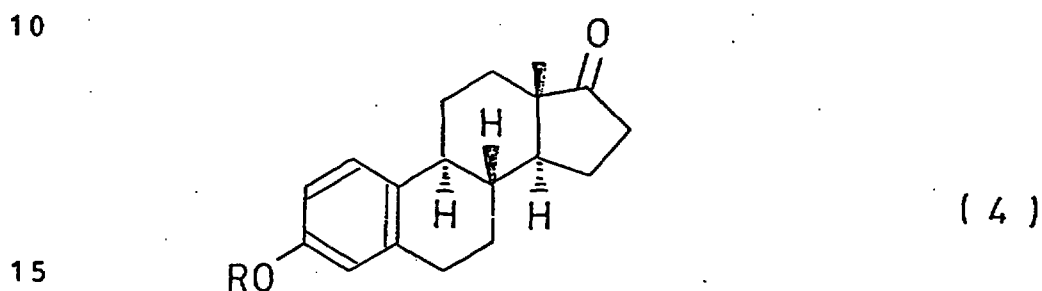
wherein R is alkyl of 1-20 carbon atoms, by employing an asymmetric Diels-Alder reaction, obtaining a compound (3)

35

represented by the formula:

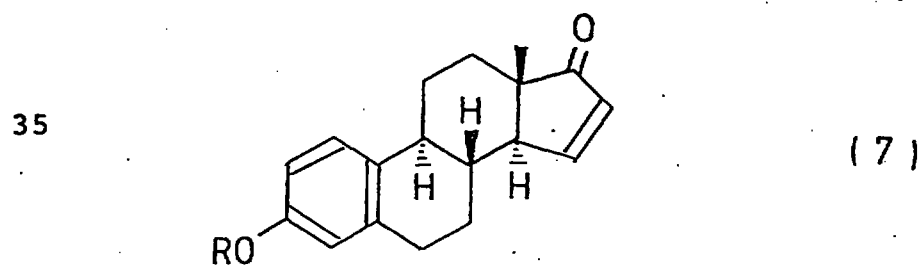
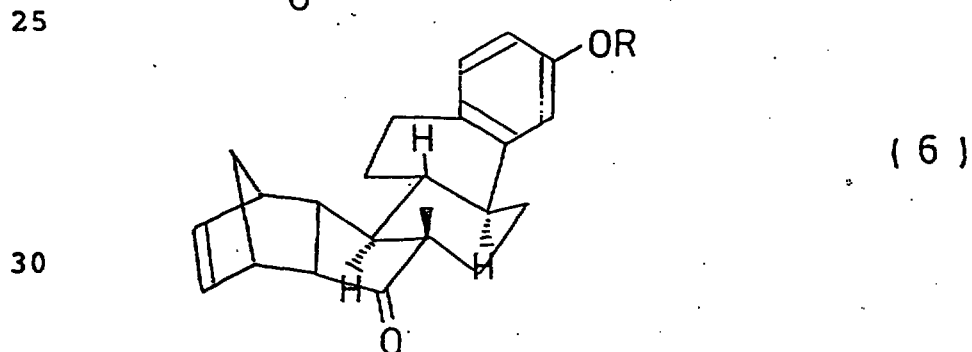
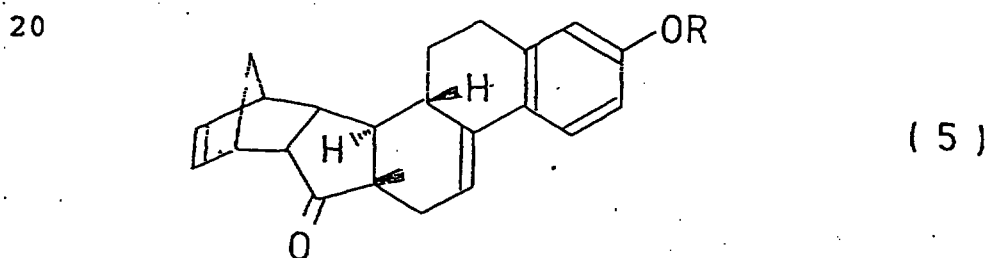


wherein R is the same as described above, and obtaining a (+)-estrone derivative represented by the formula:



wherein R is the same as described above.

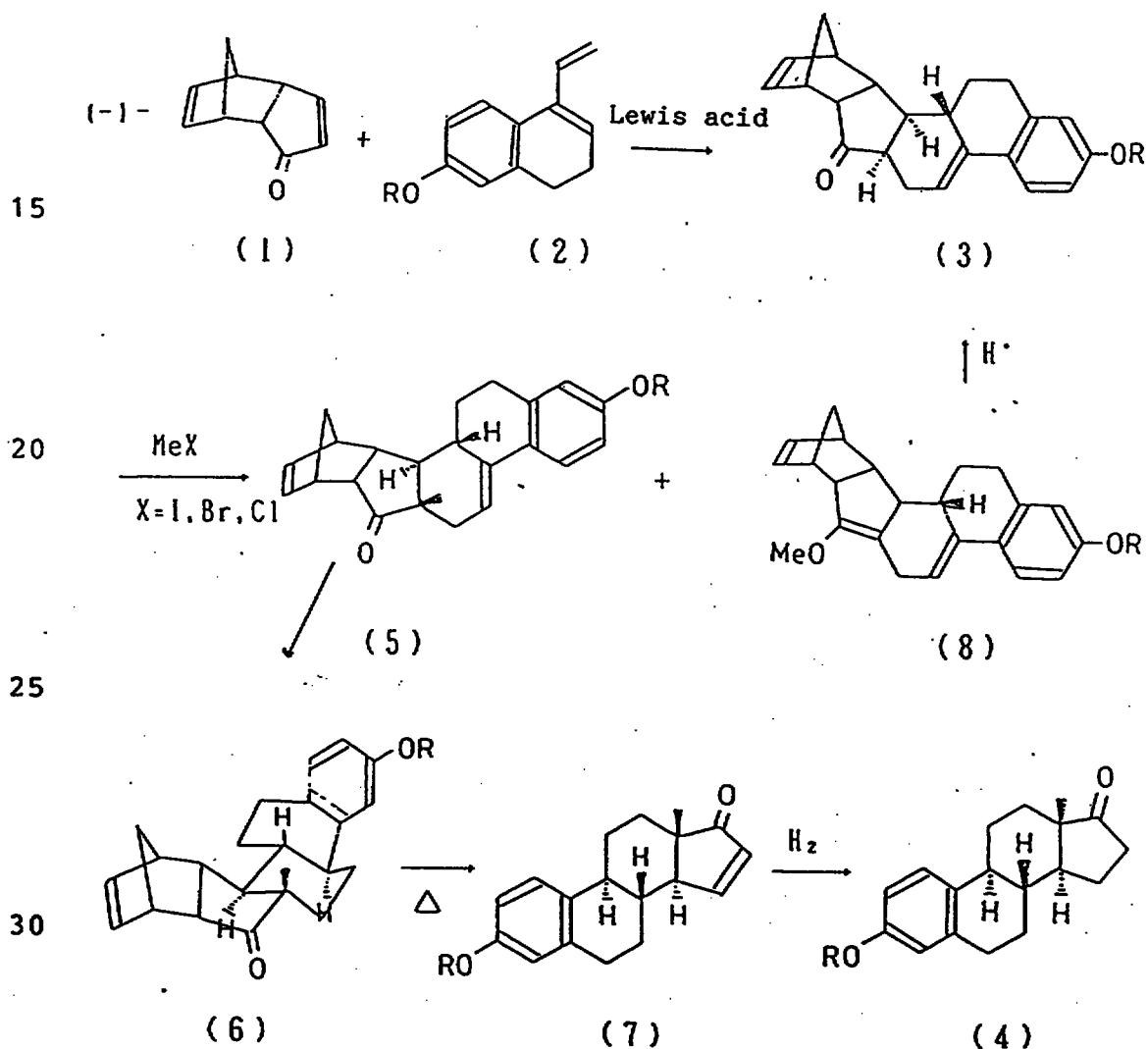
Preferably, in the steps to obtain (+)-estrone derivatives, (4) from compound (3), intermediates are represented by the formulas:



5

Wherein R is alkyl of 1-20 carbon atoms.

The reaction steps of the production method of the
10 present invention are as follows:



The starting material of the present invention, (-)-
35 tricyclo [5.2.1.0^{2.6}] deca-4,8-diene-3-one (1) is ob-

obtainable by oxidising dicyclopentadiene with selenic oxide, reacting the obtained racemic-tricyclo [5.2.1.0^{2.6}] deca-3-hydroxy-4,6-diene with an acylating agent in the presence of lipase by a transesterification reaction
5 (Japanese Patent Unexamined Publication No. 3-98597(1991), or acetylating the racemic-tricyclo [5.2.1.0^{2.6}] deca-3-hydroxy-4,6 diene and hydrolyzing the obtained compounds in the presence of lipase by hydrolyzing reaction (J, Chem. Soc, Chem, Commun.) 1989, 271), and
10 optically resolving the obtained alcohols.

The obtained (-)-tricyclo [5.2.1.0^{2.6}] deca-4,8-diene-3-one (1) and 4-vinyl-7-alkoxy-1,2-dihydronaphthalene (2) which is obtainable by a method of Schmidt et al. (Liebigs Ann. Chem., 536, 196 (1938); ibid
15 537, 246 (1939)) can be reacted in the presence of a Lewis acid by an asymmetric Diels-Alder reaction, and the compound (3) obtained. As the Lewis acid used here, diethyl aluminum chloride is preferred, but a compound such as titanium tetrachloride or aluminum
20 chloride, which can catalyse the reaction controlling the configuration, can be used. The reaction temperature is between -78°C to -10°C, preferably -30°C.

Hydrocarbons or halogenated solvents can be used as the reaction solvents, especially preferably n-hexane and
25 dichloromethane.

Although the reaction time shall be altered by the treating amounts, usually it is 12-96 hours, preferably 24-36 hours.

The obtained compound (3) can be converted to the
30 compound (5) by methylation with methyl iodide in the presence of a base. As the base, potassium t-butoxide is preferred. However, any kind of base by which the methylation proceeds can be used. Further, methyl bromide or methyl chloride can be used as a methylation agent.

35 The compound (8) which is an O-methyl compound ob-

tained as a byproduct in this step can be separated off by column chromatography or the like. The separated compound (8) can be treated with hydrochloric acid at 0°C to easily return to the compound (3), and can be used as a
5 reaction intermediate of (+)-estrone.

The compound (6) is obtainable by treating the compound (5) with trifluoroacetic acid and triethyl silane.

Further, by heating the compound (6), the compound (7) is obtainable by a retro-Diels-Alder reaction.

10 At the final step, the compound (7) can be reduced at an unsaturated bond by catalytic hydrogenation, and the objective (+)-estrone derivatives (4) obtained. A catalyst such as Raney nickel or the like, preferably palladium carbon, can be used.

15 As described above, (+)-estrone derivatives having high total yield can be obtained by reduced reaction steps from the starting materials of dicyclopentadiene derivatives (1). Considering the recovery of the compound (8), the yield of the (+)-estrone derivatives becomes
20 better.

The following examples illustrate the present invention more specifically. However, the present invention is not limited by these examples.

25 Example 1

To 25 ml of dichloromethane, 1.72 g (11.8 mmol) of (-)-tricyclo [5. 2. 1. 0^{2.6}] deca-4,8-diene-3-one (1) and 2.63 g (14.1 mmol) of 4-vinyl-7-methoxy-1,2-dihydronaphthalene (2) are dissolved, and the mixture was
30 cooled to -30°C. To the solution, 15 ml (14.1 mmol) of diethyl aluminium chloride (0.94 M, n-hexane solution) was dropwisely added. After being stirred for 32 hours at -30°C, 5% hydrochloric acid was added, and the mixture was extracted with dichloromethane. Then, the dichloro-
35 menthane layer was succesively, washed saturated sodium

bicarbonate solution and saturated sodium chloride solution, and dried over magnesium sulfate. After dichloromethane was distilled off, the residue was subjected to silica gel column chromatography, and 3.1 g (yield 81.5%) of the compound (3) was obtained.

The physical properties of the compound are as follows:

$[\alpha]_D^{31} -168.3^\circ$ (c 1.01, CHCl_3).

IR (film) ν_{max} 1730, 1605 cm^{-1} .

^1H -NMR (500 MHz, CDCl_3) δ 1.35 (1H, d, $J=8.5$ Hz), 1.51 (1H, d, $J=7.9$ Hz), 1.84 (1H, ddd, $J=17.1, 12.2, 4.9$ Hz), 1.95-2.02 (1H, m), 2.16-2.27 (2H, m), 2.36-2.51 (3H, m), 2.58-2.62 (1H, m), 2.72-2.91 (4H, m), 3.09-3.12 (1H, m), 3.80 (3H, s), 6.15-6.22 (3H, m), 6.66 (1H, d, $J=8.6$ Hz), 7.47 (1H, d, $J=8.6$ Hz).

MS m/z 332 (M^+), 266 (100%).

Elemental analysis :

Calculated for $\text{C}_{23}\text{H}_{24}\text{O}_2$: C 83.10, H 7.28.

Found : C 83.16, H 7.34.

Example 2

To a solution of 560 mg (1.96 mmol) of the compound (3) in 8 ml of dimethoxyethane, 37.8 mg (3.37 mmol) of potassium *t*-butoxide was dropwisely added at room temperature, and the mixture was stirred for 12 minutes. 1.1 ml (17 mmol) of methyl iodide was added under cooling with ice, followed by stirring for 12 minutes, adding saturated sodium bicarbonate solution, and extracting the mixture with ether. The organic layer was washed with saturated sodium chloride solution and dried over magnesium sulfate, the solvent was distilled off, and the residue was subjected to silica gel column chromatography using an eluent of ether/*n*-hexane (1/1). 334 mg (yield 57%) of the compound (5) and 123 mg (yield 21%) of the compound (8) were obtained from corresponding fractions. The compound (5) was recrystallized from methanol to obtain

colorless needle crystals.

The physical properties of the compound are as follows:

[α]_D³¹+130° (c 0.665, CHCl₃).
5 IR (film) $\nu_{\max}$ 1735, 1606 cm⁻¹.
¹H-NMR (90 MHz, CDCl₃) J, 1.09 (3H, s,), 1.48-2.65 (9H, m), 2.80-3.21 (5H, m), 3.78 (3H, s), 5.81-6.06 (2H, m), 6.10-6.28 (1H, m), 6.57-6.79 (2H, m), 7.39 (1H, d, J=8.3 Hz).

10 MS m/z 246 (M⁺ 100%).

Elemental analysis :

Calculated for C₂₄ H₂₆ O₂ : C 83.20, H 7.56.

Found : C 83.21, H 7.78.

Example 3

15 To a solution of 304 mg (0.878 mmol) of the compound (5) in 6 ml of dichloromethane, 0.68 ml (8.83 mmol) of trifluoroacetic acid and 0.70 ml (4.38 mmol) of triethyl silane were dropwisely added, and the mixture was stirred for 20 hours at room temperature, followed by adding
20 saturated sodium carbonate under cooling with ice, and extracting the mixture with dichloromethane. The extract was washed with saturated sodium chloride and dried over magnesium sulfate. The solvent was distilled off under reduced pressure, the residue was subjected to silica gel
25 column chromatography using an eluent of ether/n-hexane (1/15), and 2.65 mg (yield 87%) of the compound (6) was obtained from the fraction. The product was recrystallized from methanol to obtain colorless needle crystals.

The physical properties are as follows.

30 Melting point : 173-174°C.

[α]_D³¹+126° (c 0.96, CHCl₃).

IR (nujol) $\nu_{\max}$ 1728 cm⁻¹.

¹H-NMR (500 MHz, CDCl₃) J, 1.07 (3H, s,), 1.35-1.48 (3H, m), 1.52-1.74 (5H, m), 2.07-2.18 (2H, m), 2.25-2.32 (1H, m), 2.77 (1H, tb, J=10.4, 4.3 Hz), 2.87-2.98 (3H,

35

m), 3.08 (1H, br, s), 3.24 (1H, dd, J=10.3, 4.2 Hz), 3.77 (3H, s), 6.02 (1H, dd, J=5.5, 3.0 Hz), 6.22 (1H, dd, J=5.5, 3.0 Hz), 6.64 (1H, d, J=3.0 Hz), 6.70 (1H, dd, J=11.0, 2.5 Hz), 7.16 (1H, d, J=9.1 Hz).

5 MS m/z 348 (M^+), 282 (100%).

Elemental analysis :

Calculated for $C_{24}H_{28}O_2$: C 82.72, H 8.10

Found : C 82.55, H 8.10.

Example 4

10 13 mg (0.037 mmol) of the compound (6) and 1 ml of diphenyl ether were heated and refluxed for 1.5 hours. The reaction solution was subjected to silica gel column chromatography, and 8 mg (yield 76%) of the enone compound (7) was obtained. 4 mg of 10% paradium carbon was
15 added to ethanol solution of 39 mg (0.14 mmol) of the enone compound, and the mixture was stirred for 50 minutes in a stream of hydrogen. After filtering with cerite, the filtrate was concentrated under reduced pressure. The residue was subjected to silica gel column
20 chromatography using an eluent of ether/n-hexane (1/6), and 33 mg (yield 84%) of estrone methyl ether (4) was obtained from the fraction.

The physical properties of the compound are as follows.

25 Melting point : 174-175.5°C.

$[\alpha]_D^{33} +159^\circ$ (c 0.72, $CHCl_3$).

IR (nujol) ν_{max} 1735 cm^{-1} .

1H -NMR (90 MHz, $CDCl_3$) J, 0.88 (3H, s), 1.20-2.51 (13H, m), 2.72-2.98 (2H, m), 3.77 (3H, s), 6.54-6.67 (2H, m), 6.55-6.76 (1H, m), 7.20 (1H, d, J=8.3 Hz).
30

MS m/z 248 (M^+ 100%).

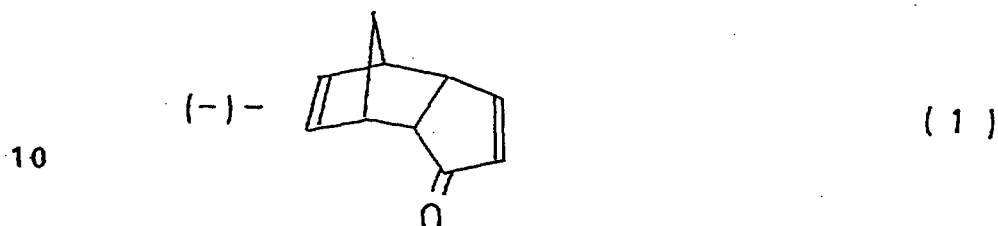
Example 5

To 5 ml of a mixture solvent of 10% HCl-THF (1:3) having a temperature of 0°C, 123 mg of the compound (8)
35 (melting point 103-105°C, $[\alpha]_D^{33} +215^\circ$ (c 1.0.1, $CHCl_3$))

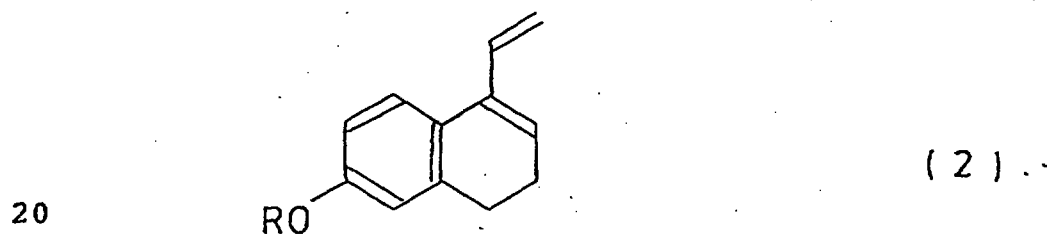
was dissolved. Upon slowly warming from 0°C to room temperature, the mixture was stirred for 1.5 hours. Saturated sodium bicarbonate was added to the mixture under cooling with ice, the neutralized mixture was
5 extracted with dichloromethane, and the extract layer was washed with sodium chloride and dried over magnesium sulfate. After dichloromethane was distilled off, the residue was subjected to silica gel column chromatography, and 100 mg of the compound (3) was quantitatively
10 obtained.

Claims

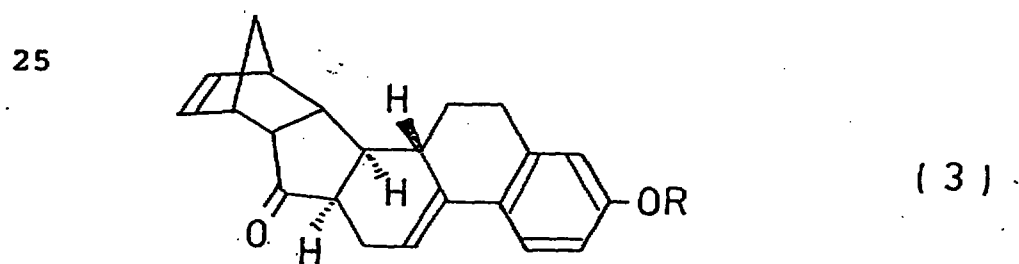
1. A method for producing a (+)-estrone derivative
 5 comprising starting from (-)-tricyclo [5.2.1.0^{2,6}] deca-
 4,8-diene-3-one (1) represented by the formula:



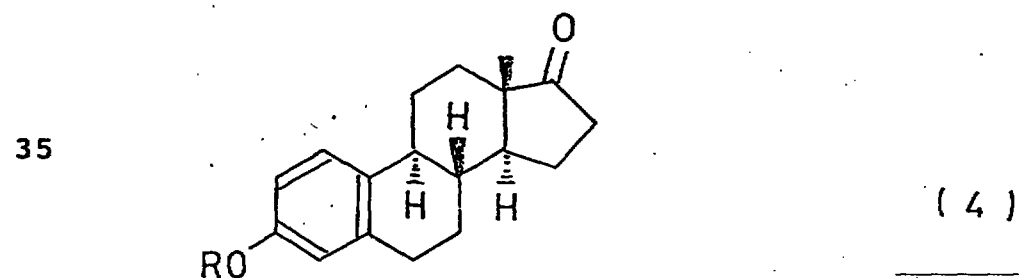
- by employing an asymmetric Diels-Alder reaction, reacting
 the compound (1) with 4-vinyl-7-alkoxy-1,2-
 15 dihydronaphthalene (2) represented by the formula:



wherein R is alkyl of 1-20 carbon atoms, obtaining a
 compound (3) represented by the formula:

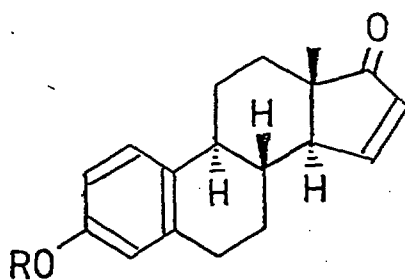
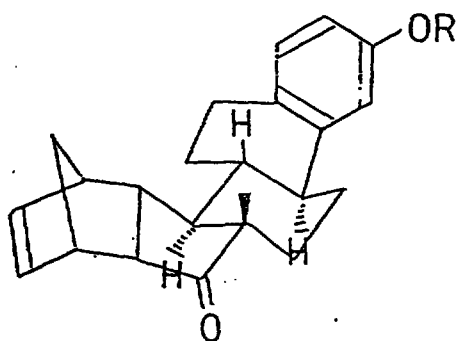
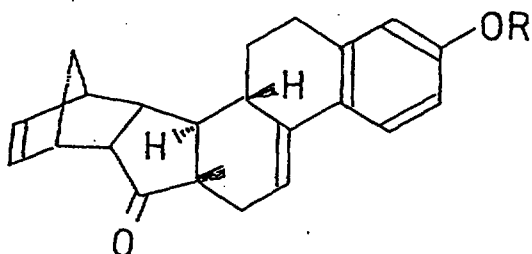


- 30 wherein R is the same as described above, and obtaining a
 (+)-estrone derivative represented by the formula:



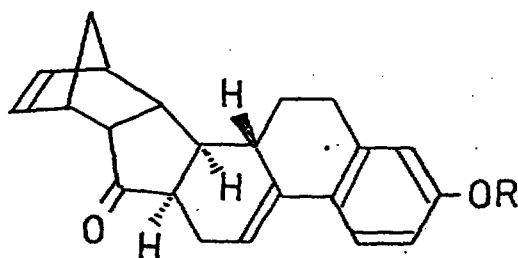
wherein R is the same as described above.

2. A method according to claim 1 for obtaining the (+)-estrone (4) from the compound (3) wherein the intermediates are represented by the formulas:



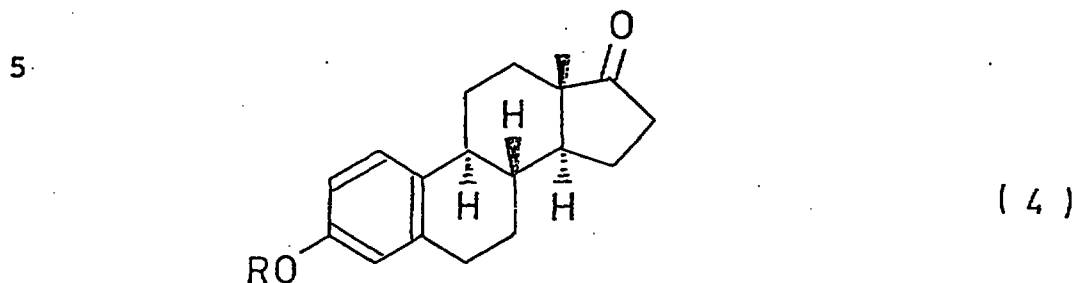
wherein R is alkyl of 1-20 carbon atoms.

3. A compound represented by the formula:



wherein R is alkyl of 1-20 carbon atoms.

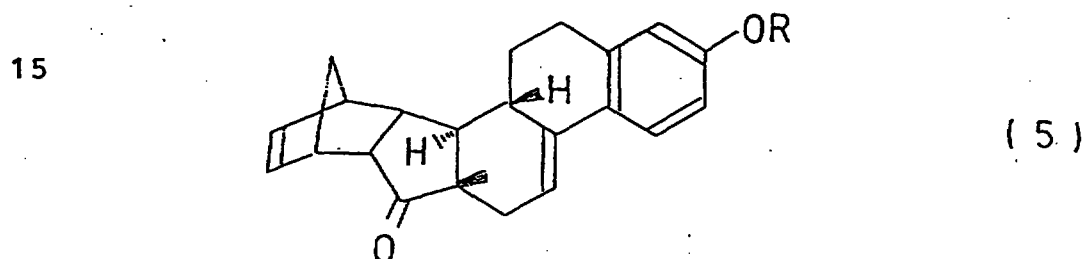
4. A compound represented by the formula:



10

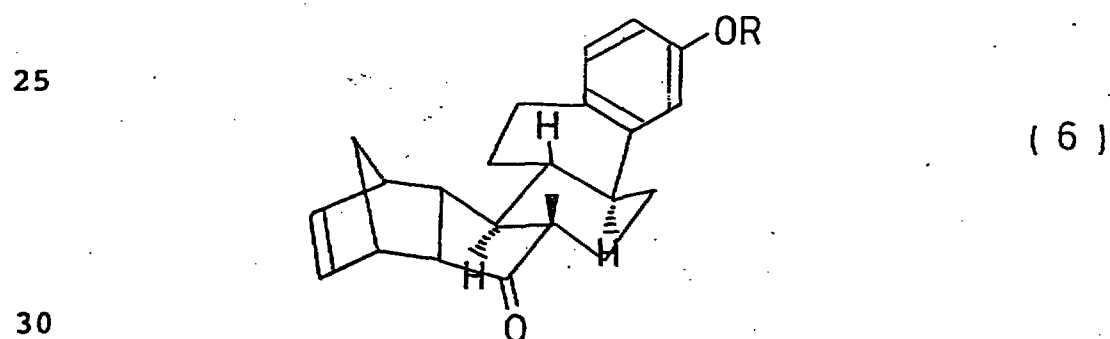
wherein R is alkyl of 1-20 carbon atoms.

5. A compound represented by the formula:



20 wherein R is alkyl of 1-20 carbon atoms.

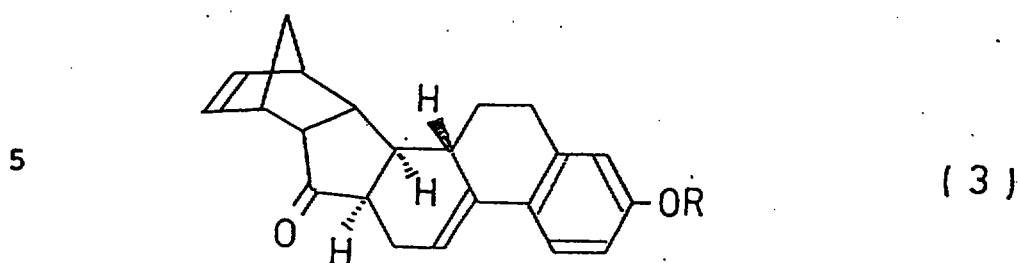
6. A compound represented by the formula:



wherein R is alkyl of 1-20 carbon atoms.

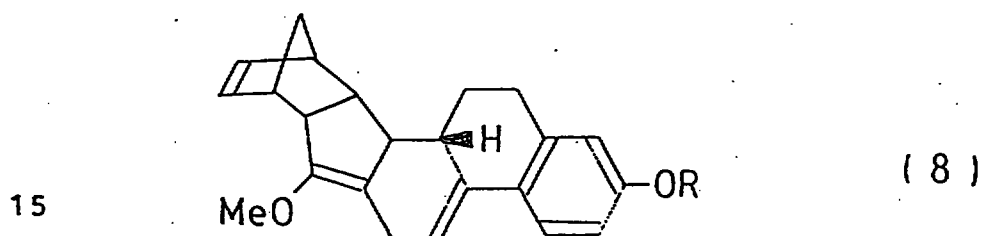
7. A method for producing the compound (3) represented
35 by the formula:





wherein R is alkyl of 1-20 carbon atoms, comprising
reacting a compound (8) represented by the formula:

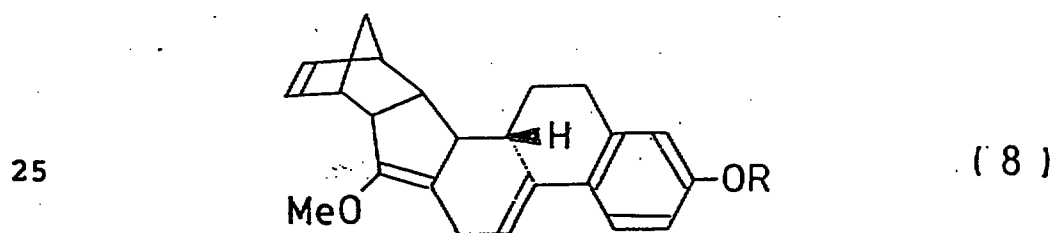
10



15

wherein R is alkyl of 1-20 carbon atoms, with an acid to
convert into the compound (3).

20 8. A compound represented by the formula:



25

wherein R is alkyl of 1-20 carbon atoms.

30

