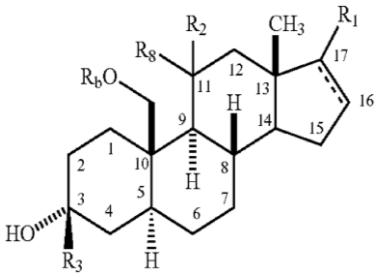
receptors and enhancement of GABAA receptors appear to play important roles in mediating the acute effects of ethanol in the nervous system, while related studies suggest that GABAergic neurosteroids may be involved in some of the pharmacological effects of ethanol and that neuroactive steroids may be useful in treating ethanol withdrawal.

[0007] In view of the foregoing, it is clear that there are a number of potentially advantageous uses for neurosteroids. As a result, there is a continuing need for the further synthesis and understanding of new neuroactive steroids, particularly those having utility as an anesthetic and/or in the treatment of a disorder relating to GABA function and activity.

Summary of the Disclosure

[0007a] In an aspect, there is provided a process for preparing a sterol of Formula (I-g):



(I-g)

or a pharmaceutically acceptable salt thereof,

wherein:

R_1 is (C_1-C_4 alkyl)-O, spirooxirane, cyano, =O, nitro, (C_1-C_4 alkyl)C(O), or HO(C_1-C_4 alkyl)C(O);

R_2 is =O, H, or OR_a, where R_a is H, optionally substituted C_1-C_4 alkyl, or optionally substituted aryl, with the proviso that when R_2 is =O, R_8 is not present;

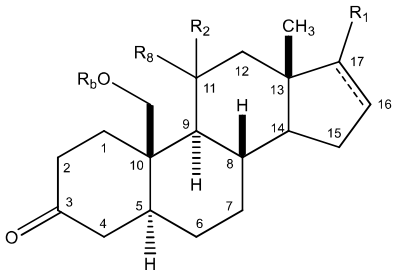
R_3 is H, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, or optionally substituted aryl;

R_b is methyl;

R_8, when present, is H or optionally substituted C_1-C_4 alkyl; and

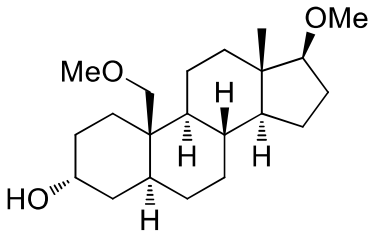
- - - denotes an optional, additional C-C bond, resulting in a C=C bond between C_{16}-C_{17}, with the proviso that when present, the R_1 is not =O or spirooxirane;

the process comprising reducing a ketone form thereof having the structure:

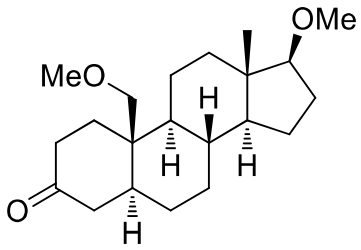


.

[0007b] In another aspect, there is provided a process for preparing a compound of the formula:

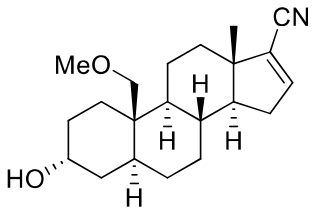


or a pharmaceutically acceptable salt thereof, comprising reducing (5α,17β)-17,19-dimethoxyandrostan-3-one having the structure:

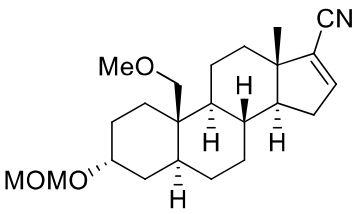


or a pharmaceutically acceptable salt thereof.

[0007c] In another aspect, there is provided a process for preparing a compound of the formula:



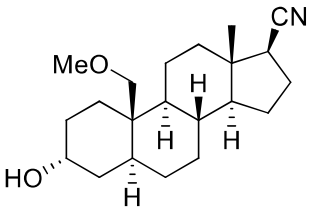
or a pharmaceutically acceptable salt thereof, comprising deprotecting the compound (3α,5α)-19-methoxy-3-(methoxymethoxy)-androst-16-ene-17-carbonitrile having the structure:



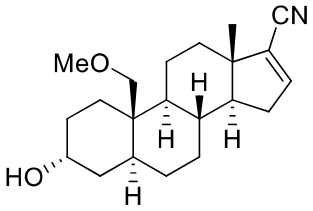
,

or a pharmaceutically acceptable salt thereof.

[0007d] In another aspect, there is provided a process for preparing a compound of the formula:



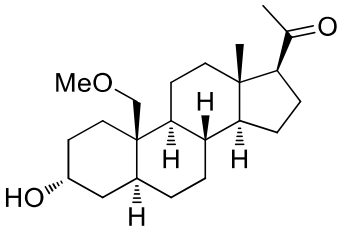
or a pharmaceutically acceptable salt thereof, comprising hydrogenating the compound (3α,5α)-3-hydroxy-19-methoxyandrost-16-ene-17-carbonitrile having the structure:



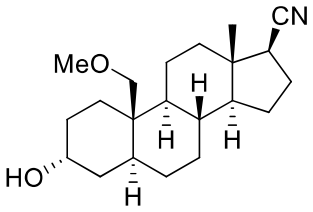
,

or a pharmaceutically acceptable salt thereof.

[0007e] In another aspect, there is provided a process for preparing a compound of the formula:



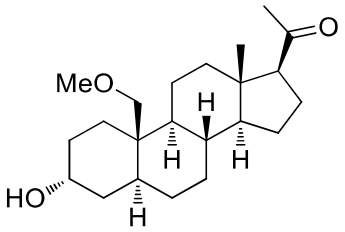
or a pharmaceutically acceptable salt thereof, comprising reacting a compound (3α,5α,17β)-3-hydroxy-19-methoxyandrostane-17-carbonitrile having the structure:



,

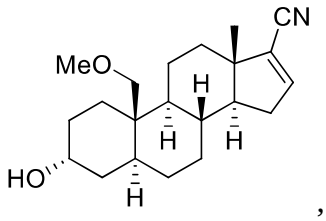
or a pharmaceutically acceptable salt thereof, with a Grignard reagent.

[0007f] In another aspect, there is provided a process for preparing a compound of the formula:



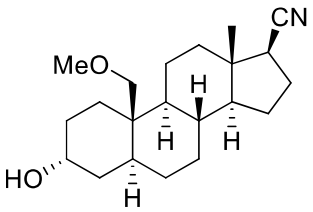
or a pharmaceutically acceptable salt thereof, comprising

(i) hydrogenating the compound (3α,5α)-3-hydroxy-19-methoxyandrost-16-ene-17-carbonitrile having the structure:



,

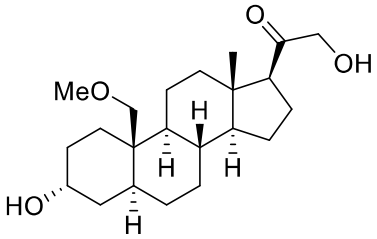
to form (3α,5α,17β)-3-hydroxy-19-methoxyandrostane-17-carbonitrile having the structure



; and

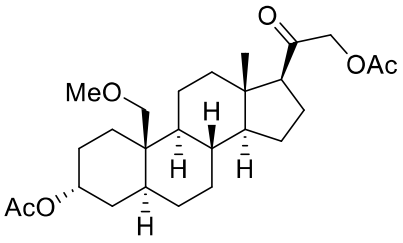
(ii) reacting (3α,5α,17β)-3-hydroxy-19-methoxyandrostane-17-carbonitrile, or a pharmaceutically acceptable salt thereof, with a Grignard reagent.

[0007g] In another aspect, there is provided a process for preparing a compound of the formula:



,

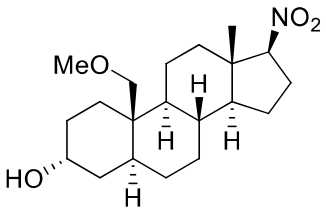
or a pharmaceutically acceptable salt thereof, comprising deprotecting the compound (3α,5α)-3,21-bis(acetyloxy)-19-methoxylpregnan-20-one having the structure:



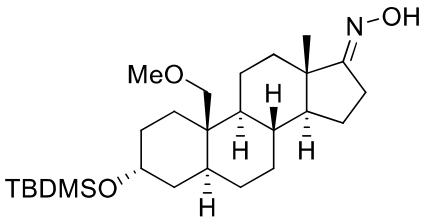
,

or a pharmaceutically acceptable salt thereof.

[0007h] In another aspect, there is provided a process for preparing a compound of the formula:



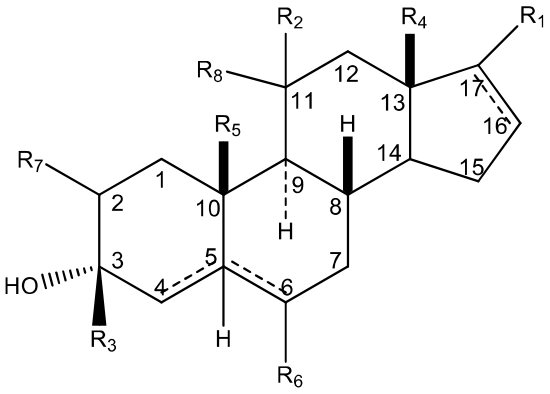
or a pharmaceutically acceptable salt thereof, comprising deprotecting and oxidizing the compound (3α,5α)-3-[[(dimethylethyl)dimethylsilyl]oxy]-19-methoxyandrostan-17-one, oxime having the structure:



,

or a pharmaceutically acceptable salt thereof.

[0008] In one example, the present disclosure is directed to a compound having a structure of Formula (I):



(I)

or a pharmaceutically acceptable salt thereof;

wherein:

[0009] R1 is selected from (C1-C4 alkyl)-O, spirooxirane, cyano, =O, nitro, (C1-C4 alkyl)C(O), and HO(C1-C4 alkyl)C(O), with R1 preferably being in the beta position when other than =O, and/or in one or more preferred embodiments C1-C4 alkyl being methyl, R1 therefore being is selected from methoxy, spirooxirane, cyano, =O, nitro, CH3C(O)- and OHCH2C(O)-;

[0010] R2 is =O, H, or ORa, where Ra is selected from H, optionally substituted C1-C4 alkyl, or optionally substituted aryl, with the proviso that when R2 is =O, R8 is not present;

[0011] R3 is H, optionally substituted C1-C4 alkyl, optionally substituted C2-C4 alkenyl, optionally substituted C2-C4 alkynyl, or optionally substituted aryl;

[0012] R4 is independently selected from H and unsubstituted C1-C4 alkyl;

[0013] R5 is substituted C1-C4 alkyl, optionally substituted C2-C4 alkenyl, or optionally substituted C2-C4 alkynyl (and in particular is alkoxy-substituted methyl, or even more particular is –CH2–ORb, where Rb is C1-C4 alkyl, or even still more particularly is –CH2–OCH3);

[0014] R6 is H, optionally substituted C1-C4 alkyl, or optionally substituted C1-C4 alkoxy;

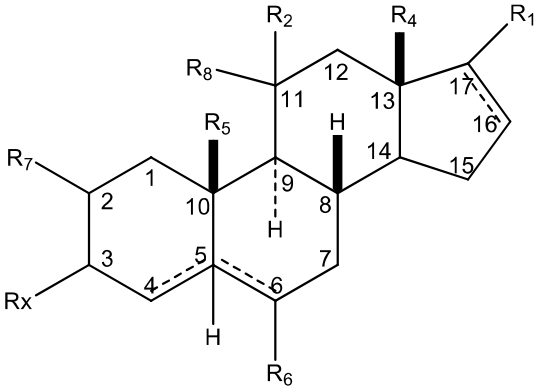
[0015] R7 is H, optionally substituted C1-C4 alkoxy, or an optionally substituted morpholinyl ring;

[0016] R8, when present, is H or optionally substituted C1-C4 alkyl;

[0017] - - - denotes an optional, additional C-C bond, resulting in either a C=C bond between C4-C5 or C5-C6, with the proviso that when present, the R5-H substituent is not present; and,

[0018] - - - denotes an optional, additional C-C bond, resulting in a C=C bond between C16-C17, with the proviso that when present, the R1 is not =O.

[0019] The present disclosure is further directed to a pharmaceutically acceptable salt of the noted compounds, or alternatively to prodrugs thereof. In one particular example, the present disclosure is directed to a compound having a structure of Formula (II):



(II)

or a pharmaceutically acceptable salt thereof;

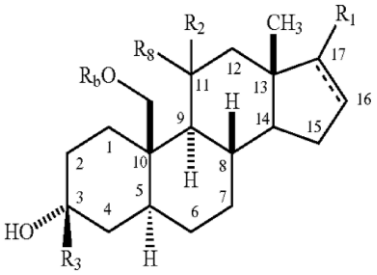
wherein:

[0020] R_1 is selected from (C1-C4 alkyl)-O, spirooxirane, cyano, =O, nitro, (C1-C4 alkyl)C(O), and HO(C1-C4 alkyl)C(O), with R1 preferably being in the beta position when other than =O, and/or in one or more preferred embodiments C1-C4 alkyl being methyl, R1 therefore being is selected from methoxy, spirooxirane, cyano, =O, nitro, CH3C(O)- and OHCH2C(O)-;

Claims

What is claimed is:

1. A process for preparing a sterol of Formula (I-g):



(I-g)

or a pharmaceutically acceptable salt thereof,

wherein:

R_1 is (C_1-C_4 alkyl)-O, spirooxirane, cyano, =O, nitro, (C_1-C_4 alkyl)C(O), or HO(C_1-C_4 alkyl)C(O);

R_2 is =O, H, or OR_a, where R_a is H, optionally substituted C_1-C_4 alkyl, or optionally substituted aryl, with the proviso that when R_2 is =O, R_8 is not present;

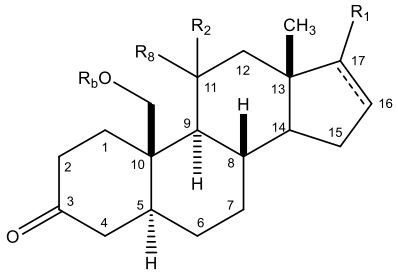
R_3 is H, optionally substituted C_1-C_4 alkyl, optionally substituted C_2-C_4 alkenyl, optionally substituted C_2-C_4 alkynyl, or optionally substituted aryl;

R_b is methyl;

R_8, when present, is H or optionally substituted C_1-C_4 alkyl; and

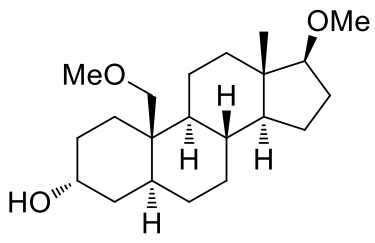
- - - denotes an optional, additional C-C bond, resulting in a C=C bond between C_{16}-C_{17}, with the proviso that when present, the R_1 is not =O or spirooxirane;

the process comprising reducing a ketone form thereof having the structure:

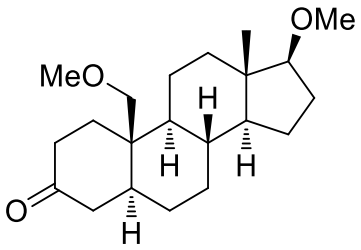


.

2. A process for preparing a compound of the formula:

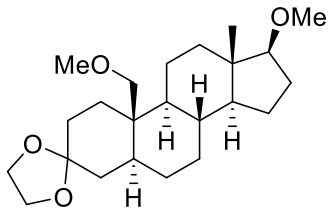


or a pharmaceutically acceptable salt thereof, comprising reducing (5α,17β)-17,19-dimethoxyandrostan-3-one having the structure:



or a pharmaceutically acceptable salt thereof.

3. The process of claim 2, further comprising reacting compound (5α,17β)-17,19-dimethoxyandrostan-3-one, cyclic 1,2-ethandiyl acetal having the structure:

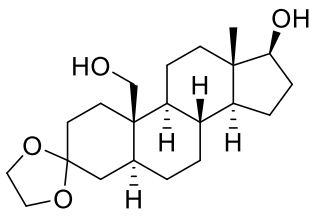


,

or a pharmaceutically acceptable salt thereof,

with p-toluenesulfonic acid (PTSA) to form (5α,17β)-17,19-dimethoxyandrostan-3-one, or a pharmaceutically acceptable salt thereof.

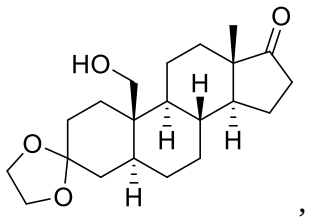
4. The process of claim 3, further comprising reacting compound (5α,17β)-17,17-dihydroxyandrostan-3-one, cyclic 1,2-ethandiyl acetal having the structure:



,

or a pharmaceutically acceptable salt thereof, with sodium hydride in the presence of iodomethane to form (5α,17β)-17,19-dimethoxyandrostan-3-one, cyclic 1,2-ethandiyl acetal.

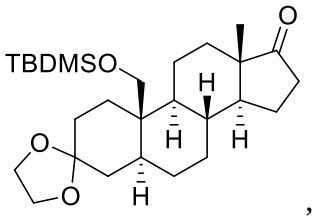
5. The process of claim 4, further comprising reacting compound (5α)-19-hydroxyandrostane-3,17-dione, 3-cyclic 1,2-ethandiyl acetal having the structure:



,

or a pharmaceutically acceptable salt thereof, with sodium borohydride to form (5α,17β)-17,17-dihydroxyandrostan-3-one, cyclic 1,2-ethandiyl acetal or a pharmaceutically acceptable salt thereof.

6. The process of claim 4, further comprising deprotecting compound (5α)-19-[[(dimethylethyl)dimethylsilyl]oxy]-androstane-3,17-dione, 3-cyclic 1,2-ethandiyl acetal, having the structure:

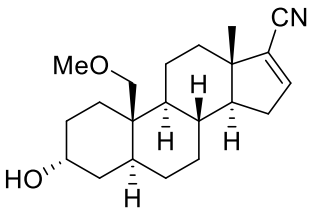


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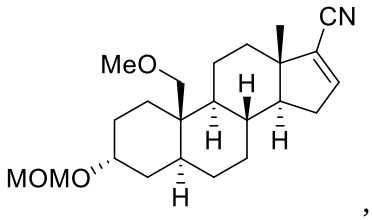
or a pharmaceutically acceptable salt thereof, to form (5α)-19-hydroxyandrostane-3,17-dione, 3-cyclic 1,2-ethandiyl acetal.

7. The process of claim 6, wherein the deprotection of (5α)-19-[[(dimethylethyl)dimethylsilyl]oxy]-androstane-3,17-dione, 3-cyclic 1,2-ethandiyl acetal or a pharmaceutically acceptable salt thereof comprises contacting (5α)-19-[[(dimethylethyl)dimethylsilyl]oxy]-androstane-3,17-dione, 3-cyclic 1,2-ethandiyl acetal or the salt thereof with tetrabutylammonium fluoride (TBAF).

8. A process for preparing a compound of the formula:



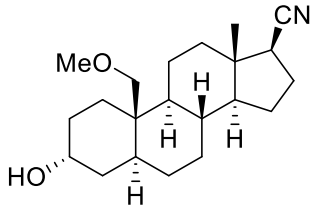
or a pharmaceutically acceptable salt thereof, comprising deprotecting the compound (3α,5α)-19-methoxy-3-(methoxymethoxy)-androst-16-ene-17-carbonitrile having the structure:



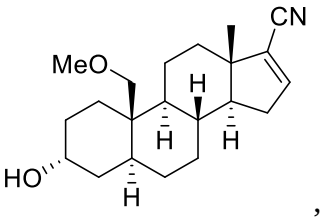
,

or a pharmaceutically acceptable salt thereof.

9. A process for preparing a compound of the formula:



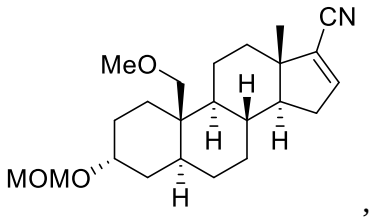
or a pharmaceutically acceptable salt thereof, comprising hydrogenating the compound (3α,5α)-3-hydroxy-19-methoxyandrost-16-ene-17-carbonitrile having the structure:



,

or a pharmaceutically acceptable salt thereof.

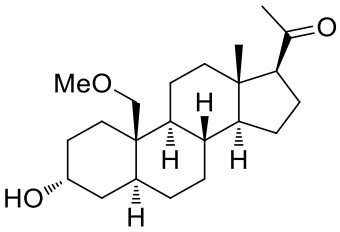
10. The process of claim 9, further comprising deprotecting the compound (3α,5α)-19-methoxy-3-(methoxymethoxy)-androst-16-ene-17-carbonitrile having the structure:



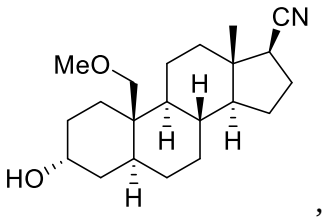
,

or a pharmaceutically acceptable salt thereof, to form (3α,5α)-3-hydroxy-19-methoxyandrost-16-ene-17-carbonitrile, or a pharmaceutically acceptable salt thereof.

11. A process for preparing a compound of the formula:



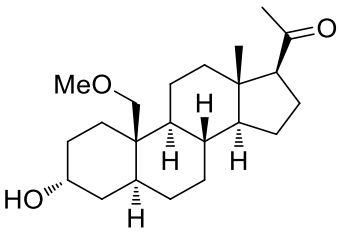
or a pharmaceutically acceptable salt thereof, comprising reacting a compound (3α,5α,17β)-3-hydroxy-19-methoxyandrostane-17-carbonitrile having the structure:



,

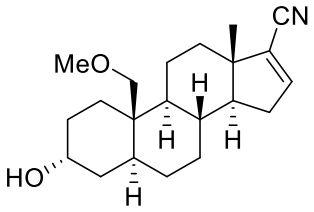
or a pharmaceutically acceptable salt thereof, with a Grignard reagent.

12. A process for preparing a compound of the formula:



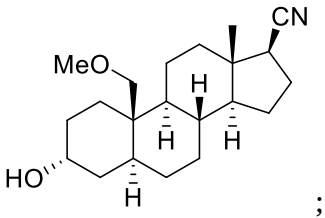
or a pharmaceutically acceptable salt thereof, comprising

(i) hydrogenating the compound (3α,5α)-3-hydroxy-19-methoxyandrost-16-ene-17-carbonitrile having the structure:



,

to form (3α,5α,17β)-3-hydroxy-19-methoxyandrostane-17-carbonitrile having the structure

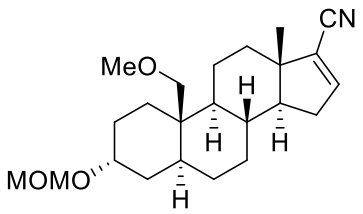


; and

(ii) reacting (3α,5α,17β)-3-hydroxy-19-methoxyandrostane-17-carbonitrile, or a pharmaceutically acceptable salt thereof, with a Grignard reagent.

13. The process of claim 11, further comprising

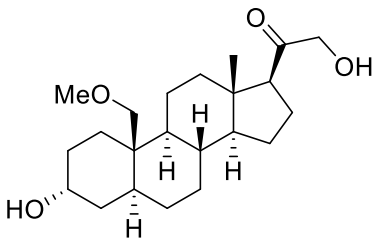
(iii)deprotecting the compound (3α,5α)-19-methoxy-3-(methoxymethoxy)-androst-16-ene-17-carbonitrile having the structure



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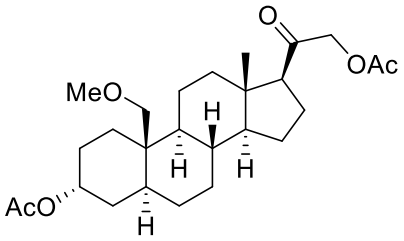
to form (3α,5α)-3-hydroxy-19-methoxyandrost-16-ene-17-carbonitrile.

14. A process for preparing a compound of the formula:



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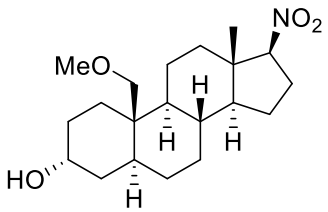
or a pharmaceutically acceptable salt thereof, comprising deprotecting the compound (3α,5α)-3,21-bis(acetyloxy)-19-methoxylpregnan-20-one having the structure:



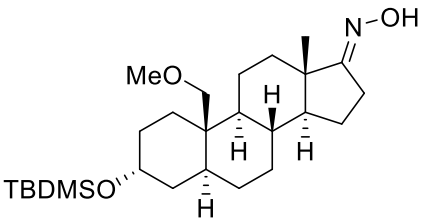
,

or a pharmaceutically acceptable salt thereof.

15. A process for preparing a compound of the formula:



or a pharmaceutically acceptable salt thereof, comprising deprotecting and oxidizing the compound (3α,5α)-3-[[(dimethylethyl)dimethylsilyl]oxy]-19-methoxyandrostan-17-one, oxime having the structure:



,

or a pharmaceutically acceptable salt thereof.