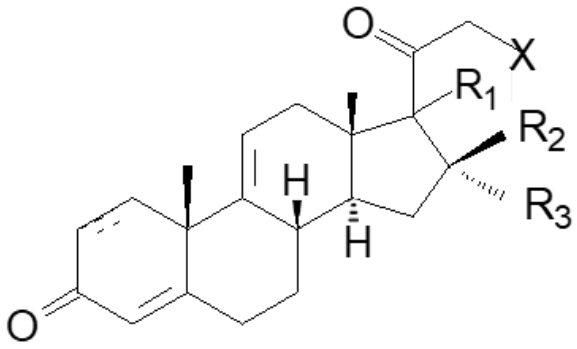
This process is difficult to control, requires the use of several toxic and hazardous chemicals and thus represents an unattractive synthesis of Vamorolone.

Overall, there is a need for a more straight forward and safe way of producing Vamorolone and other Δ9,11 steroids in high yields, and in controlled pharmaceutical purity eliminating the presence of numerous impurities and side-products (e.g. steroid-side-products) in the final product.

SUMMARY

In an aspect of the present disclosure, there is provided a use of hydroiodic acid for the preparation of a Δ9,11 steroid from a 9,11 epoxy steroid.

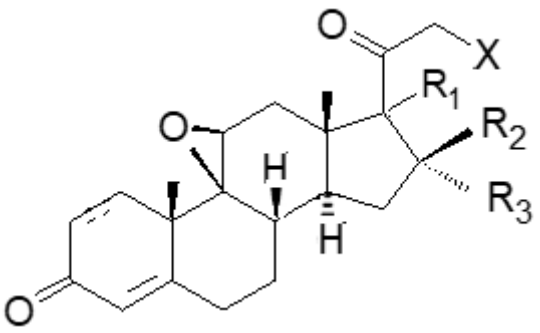
In another aspect of the present disclosure, there is provided a process for preparing a Δ9,11 steroids of the formula I,



I

wherein the dotted line is a single or a double bond; R^1 is H or OH; one of R^2 or R^3 is CH_3 and the other is H or both are H; and X is H, halo, OR, wherein R is H or $C(O)R^I$, and R^I is CF_3, C_1-C_6 alkyl, C_5-C_{12} cycloalkyl, aryl, heteroaryl or C_1-C_6 alkoxy, or NR^{II}, wherein NR^{II} is a tertiary amine, wherein the tertiary amine is part of a linear or cyclic substructure,

comprising treating an 9,11 epoxy steroid of the formula II



II

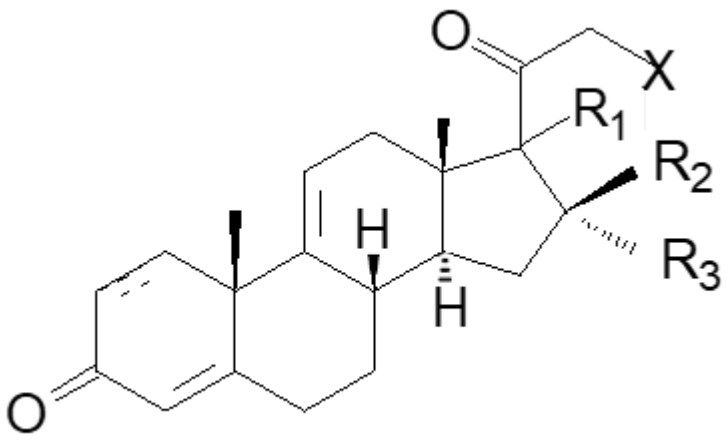
wherein the dotted line is a single or a double bond; R^1 is H or OH; one of R^2 or R^3 is CH_3 and the other is H or both are H; and X is H, halo, OR, wherein R is H or $C(O)R^I$, and R^I is CF_3, C_1-C_6 alkyl, C_5-C_{12} cycloalkyl, aryl, heteroaryl or C_1-C_6 alkoxy, or NR^{II}, wherein NR^{II} is a tertiary amine,
with hydroiodic acid, HI, to form the compound of formula I.

In a further aspect of the present disclosure, there is provided a compound by the process as disclosed herein.

In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising the compound as disclosed herein.

The present disclosure fulfils this need by providing a convenient, non-toxic and quantitative synthesis of Vamorolone and other Δ9,11 steroids. The new synthesis is surprisingly simple and significantly reduces steroid-side-products. For the synthesis of Vamorolone and other Δ9,11 steroids HI is used to deoxygenate 9,11 epoxide steroid precursors, such as the protected, e.g. acetylated, commercial 8-DM or the unprotected commercial 8-DM ((1*S*,2*S*,13*R*,14*R*,15*S*,17*S*)-14-hydroxy-14-(2-hydroxyacetyl)-2,13,15-trimethyl-18-oxapentacyclo[8.8.0.$0^{1,17}$.$0^{2,7}$.$0^{11,15}$]octadeca-3,6-dien-5-one). Δ9,11 steroids, such as 8-DM, are commercially available and protection groups (to be attached to the 21-OH moiety) can be attached using conventional synthesis means available in the art.

Accordingly, the present disclosure provides a process for preparing a Δ9,11 steroid of the formula I,

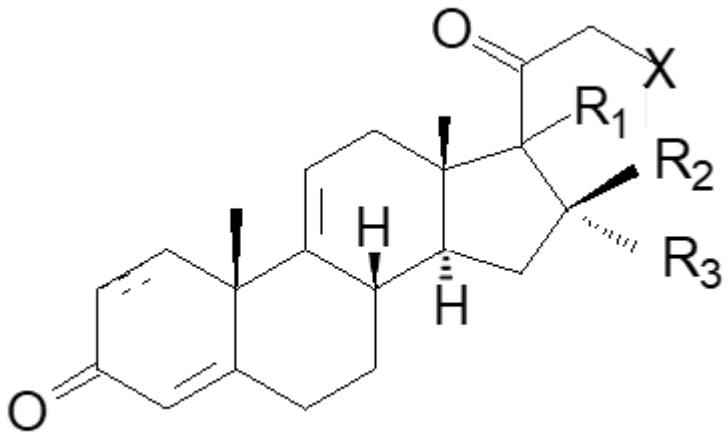


I

wherein the dotted line is a single or a double bond; R^1 is H or OH; one of R^2 or R^3 is CH_3 and the other is H or both are H; and X is H, halo, OR, wherein R is H or $C(O)R^I$, and R^I is CF_3, C_1-C_6 alkyl, C_5-C_{12} cycloalkyl, aryl, heteroaryl or C_1-C_6 alkoxy, or NR^{II}, wherein NR^{II} is a tertiary

Claims

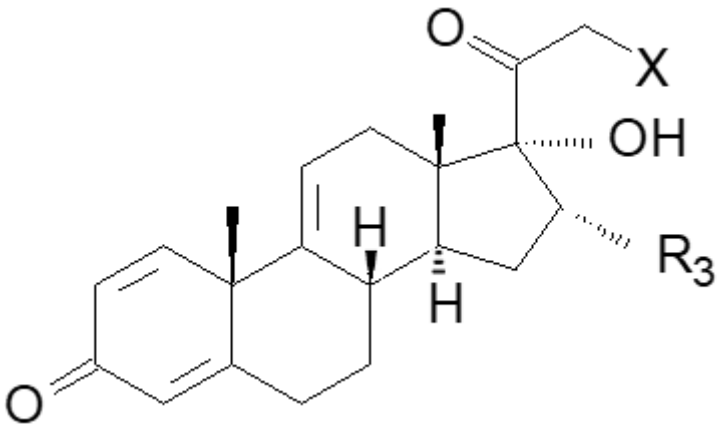
1. Use of hydroiodic acid for the preparation of a Δ9,11 steroid from a 9,11 epoxy steroid.
2. Use of claim 1, wherein the Δ9,11 steroid is a steroid of formula I,



I

wherein the dotted line is a single or a double bond; R^1 is H or OH; one of R^2 or R^3 is CH_3 and the other is H or both are H; and X is H, halo, OR, wherein R is H or $C(O)R^I$, and R^I is CF_3, C_1-C_6 alkyl or C_1-C_6 alkoxy, C_5-C_{12} cycloalkyl, aryl, heteroaryl or NR^{II}, wherein NR^{II} is a tertiary amine, wherein the tertiary amine is part of a linear or cyclic substructure.

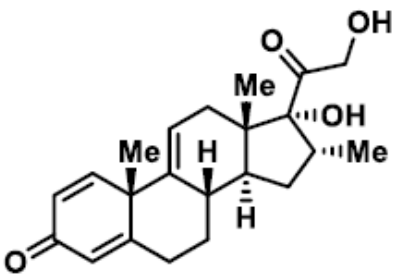
3. Use of claim 1 or 2, wherein the Δ9,11 steroid is a steroid of formula If,

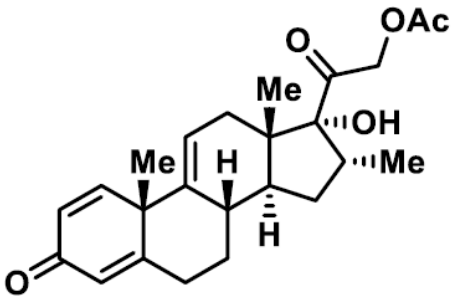


If

wherein R^3 is CH_3 or H; and X is H, halo, OR, wherein R is H or $C(O)R^I$, and R^I is CF_3, C_1-C_6 alkyl, C_5-C_{12} cycloalkyl, aryl, heteroarylor C_1-C_6 alkoxy, or NR^{II}, wherein NR^{II} is a tertiary amine, wherein the tertiary amine is part of a linear or cyclic substructure.

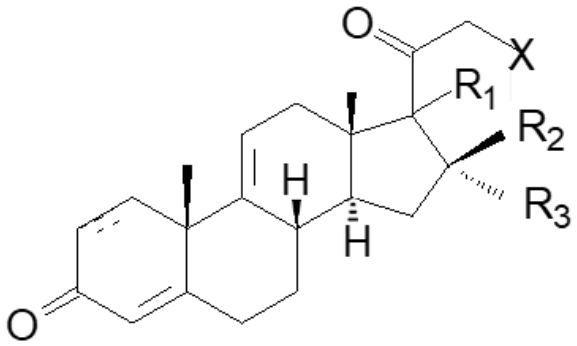
4. Use of any of claims 1-3, wherein the Δ9,11 steroid is Vamorolone or Vamorolone Acetate,





Vamorolone *Vamorolone-acetate.*

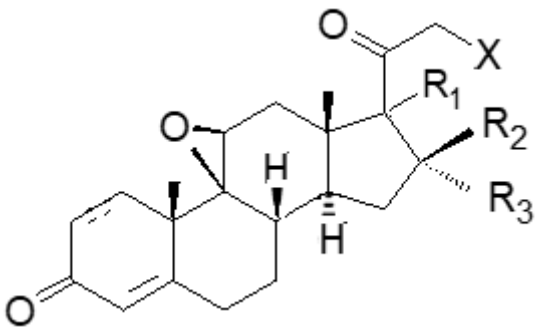
5. A process for preparing a Δ9,11 steroids of the formula I,



I

wherein the dotted line is a single or a double bond; R^1 is H or OH; one of R^2 or R^3 is CH_3 and the other is H or both are H; and X is H, halo, OR, wherein R is H or $C(O)R^I$, and R^I is CF_3, C_1-C_6 alkyl, C_5-C_{12} cycloalkyl, aryl, heteroaryl or C_1-C_6 alkoxy, or NR^{II}, wherein NR^{II} is a tertiary amine, wherein the tertiary amine is part of a linear or cyclic substructure,

comprising treating an 9,11 epoxy steroid of the formula II

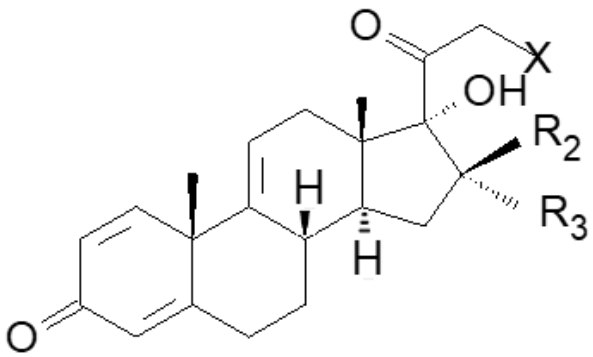


II

wherein the dotted line is a single or a double bond; R^1 is H or OH; one of R^2 or R^3 is CH_3 and the other is H or both are H; and X is H, halo, OR, wherein R is H or $C(O)R^I$, and R^I is CF_3, C_1-C_6 alkyl, C_5-C_{12} cycloalkyl, aryl, heteroaryl or C_1-C_6 alkoxy, or NR^{II}, wherein NR^{II} is a tertiary amine,

with hydroiodic acid, HI, to form the compound of formula I.

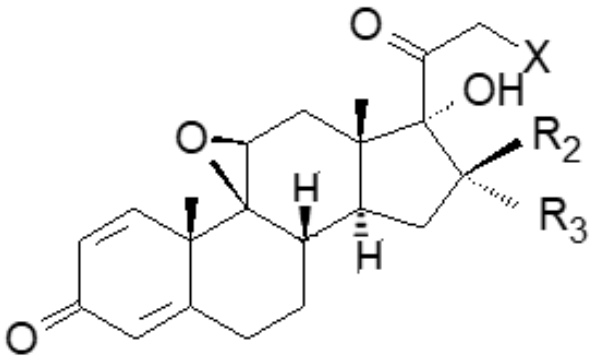
6. The process of claim 5, wherein the Δ9,11 steroid is a compound of formula Id,



Id

wherein one of R^2 or R^3 is CH_3 and the other is H or both are H; and X is H, halo, OR, wherein R is H or $C(O)R^I$, and R^I is CF_3, C_1-C_6 alkyl, C_5-C_{12} cycloalkyl, aryl, heteroarylor C_1-C_6 alkoxy, or NR^{II}, wherein NR^{II} is a tertiary amine, wherein the tertiary amine is part of a linear or cyclic substructure,

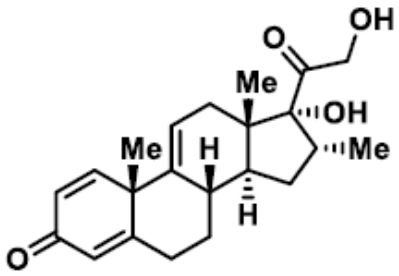
and the 9,11 epoxy steroid is a compound of formula IId,

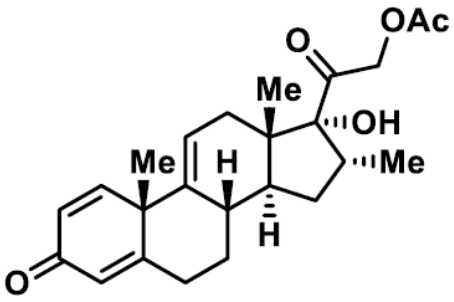


IId

wherein one of R^2 or R^3 is CH_3 and the other is H or both are H; and X is H, halo, OR, wherein R is H or $C(O)R^I$, and R^I is CF_3, C_1-C_6 alkyl, C_5-C_{12} cycloalkyl, aryl, heteroaryl or C_1-C_6 alkoxy, or NR^{II}, wherein NR^{II} is a tertiary amine, wherein the tertiary amine is part of a linear or cyclic substructure, with hydroiodic acid, HI, to form the compound of formula Id.

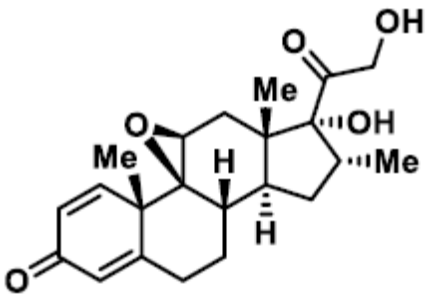
7. The process of claim 5 or 6, wherein the Δ9,11 steroid is a compound selected from Vamorolone or Vamorolone Acetate

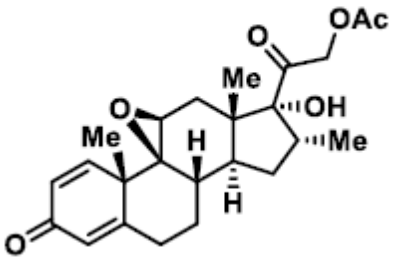




Vamorolone *Vamorolone-acetate*

and the 9,11 epoxy steroid is a compound of 8-DM and 8-DM acetate, respectively.





8-DM *8-DM-acetate*

8. The process of any of claims 5-7, wherein the Δ9,11 steroid is prepared using aqueous HI in an organic solvent and in the presence of an organic acid or without the addition of an organic acid and wherein treatment is carried out at a temperature of below 15°C.

9. The process of any of claim 8, wherein the organic solvent is MeCN, CH_2Cl_2, or Toluene; or a mixture of two or all three thereof, and
wherein the organic acid is acetic acid.

10. The process of any of claims 5-9, wherein the Δ9,11 steroid is prepared using aqueous HI, at a concentration of between 48 and 68 wt%, in toluene.

11. The process of any of claims 5-10, wherein if X is OH, the 9, 11 epoxy steroid is acetylated before the treating of the 9,11 epoxy steroid with HI.

12. The process of claim 11, wherein the Δ9,11 steroid obtained in claim 15 after treating the 9,11 epoxy steroid with HI, is de-acetylated.

13. The process of any of claims 5-12 for preparing a pharmaceutically pure Δ9,11 steroid comprising a step of recrystallization of the crude Δ9,11 steroid obtained in any of claims 2-15, in iPrOH or a mixture of iPrOH and water.

14. The compound produced by the process of any of claims 5-13.

15. The compound produced by the process of claim 13.

16. A pharmaceutical composition comprising the compound of claim 14 or 15.