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PROCESS FOR PREPARATION OF 9,11 β -EPOXIDE STEROIDS10 **BACKGROUND**

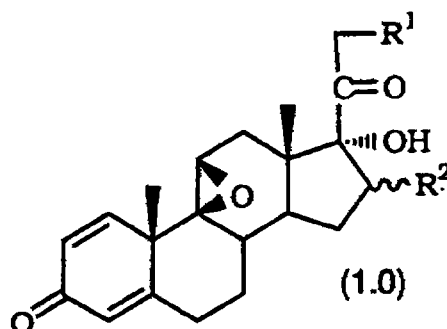
A translation of East German 268954 A1 discloses a process for preparing steroids of the pregnane series which contain a 9 α -halogen-11 β -formyloxy group. Steroids with these substituents are precursors to the respective 9 α -halo, 11 β -hydroxysteroids.

15 In view of the importance of 9 α -halo, 11 β -hydroxysteroids, processes which produce their precursors in high yield with a minimum of by-products would be a welcome contribution to the art. The claimed invention provides just such a contribution.

20 **SUMMARY OF THE INVENTION**

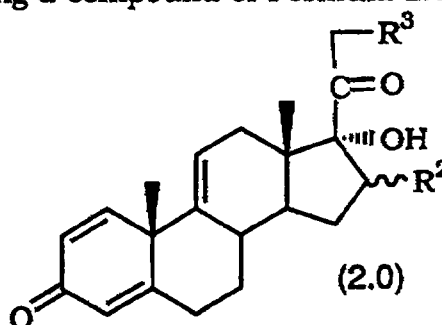
The claimed invention is directed to a process for producing 9,11 β -epoxy steroids from their 9,11-double bond precursors. The use of a minimal amount of DMF and a minimal amount of 70% HClO₄ when the 9,11-double bond precursor is
25 reacted with a suitable brominating or chlorinating agent produces the corresponding 9 α -halo-11 β -formate steroid with minimal formation of dihalo by-products. The 9 α -bromo-11 β -formate or 9 α -chloro-11 β -formate steroid intermediate is then reacted, at a low temperature, with a suitably strong base in a
30 suitable organic solvent mixture, to give the corresponding 9,11 β -epoxy steroid.

The claimed invention is directed to a process for producing an epoxy steroid of Formula 1.0:



wherein R^1 is selected from H, -OH, or Cl; and R^2 is selected from hydrogen or lower alkyl; said process comprising:

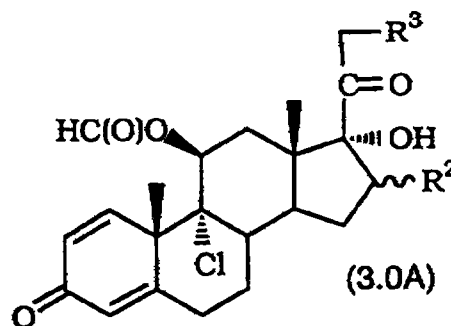
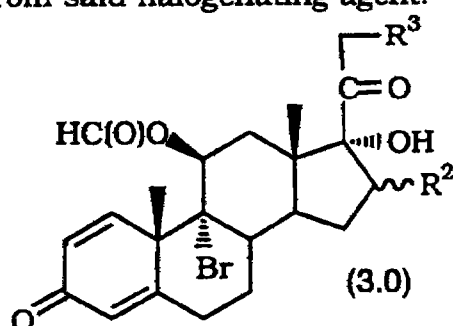
(A) reacting a compound of Formula 2.0:



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with a brominating agent selected from DBH or NBS, or a chlorinating agent selected from an N-chloroimide or N-chloroamide, said reaction being conducted in DMF containing a catalytic amount of 70% HClO_4 , at a temperature of about 0 to about +40°C, thereby producing the bromoformate of Formula 3.0 from said brominating agent or the chloroformate of Formula 3.0A from said halogenating agent:

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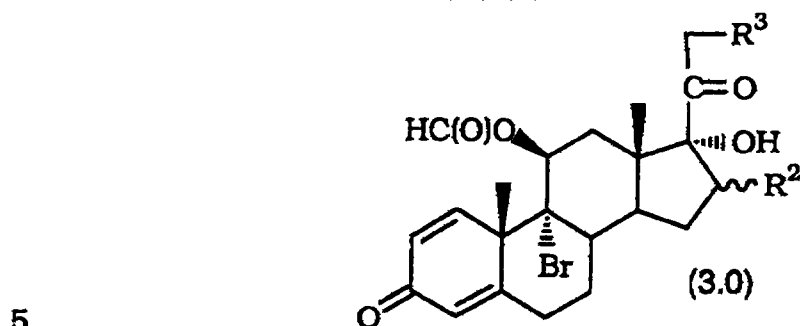
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wherein: R^2 is as defined above; and when R^1 is H then R^3 is H; and when R^1 is -OH then R^3 is a suitably protected -OH group; and when R^1 is Cl then R^3 is Cl; and

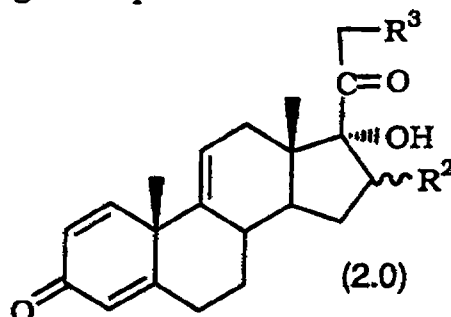
(B) reacting, at a temperature of about -20 to about +10°C, the bromoformate of Formula 3.0 or the chloroformate of Formula 3.0A with a strong base in an organic solvent mixture

comprising: (a) THF or CH_2Cl_2 and (b) a C_1 to C_6 alkanol or acetonitrile; thereby producing the epoxy steroid of Formula 1.0.

This invention is also directed to a process for producing a bromoformate of Formula 3.0 :

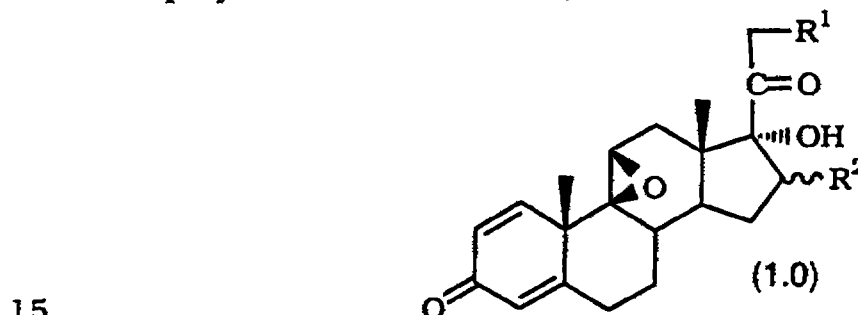


comprising reacting a compound of Formula 2.0:

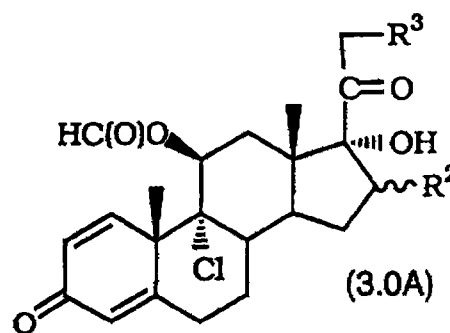
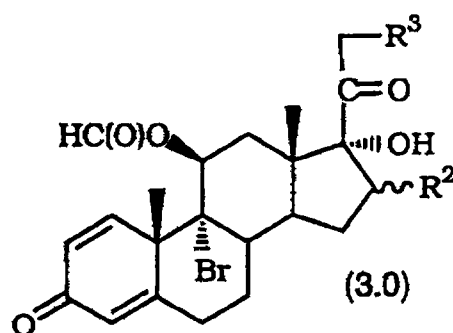


10 with a brominating agent selected from DBH or NBS, in DMF containing a catalytic amount of 70% HClO_4 , at a temperature of about 0 to about 40°C ; wherein R^2 is selected from hydrogen or lower alkyl; and R^3 is selected from H, a suitably protected -OH group, or Cl.

This invention is also directed to a process for producing an epoxy steroid of Formula 1.0



comprising reacting a bromoformate of Formula 3.0 or a chloroformate of Formula 3.0A



- with a strong base in an organic solvent mixture comprising: (a) THF or CH₂Cl₂ and (b) a C₁ to C₆ alkanol or acetonitrile, at a temperature of about -20 to about +10°C; wherein: R¹ is selected from H, -OH, or Cl; R² is selected from hydrogen or lower alkyl; and R³ is selected from H when R¹ is H, a suitably protected -OH group when R¹ is -OH, or Cl when R¹ is Cl.

DETAILED DESCRIPTION OF THE INVENTION

- The terms below, as used herein, have the stated meaning unless otherwise defined herein:

alkyl - represents straight and branched carbon chains and contains from one to twenty carbon atoms, preferably one to six carbon atoms;

- DBH - 1,3-dibromo-5,5-dimethylhydantoin;

DMF - represents dimethylformamide;

lower alkyl - represents straight or branched chain alkyl groups having from 1 to 6 carbon atoms, e.g., methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, n-pentyl, isopentyl, n-hexyl, and 2,3-dimethyl-butyl;

Meq - represents molar equivalents;

NBS - represents N-bromosuccinimide; and

THF - represents tetrahydrofuran.

- Preferably, R¹ is -OH, and R² is lower alkyl with -CH₃ being most preferred.

- R³ is (a) H when R¹ is H; (b) Cl when R¹ is Cl; and (c) a suitably protected -OH group when R¹ is OH. The suitably protected -OH group is obtained using suitable protecting groups known in the art. Suitable protecting groups are those groups which, under the reaction conditions of the epoxide formation,

are easily hydrolyzable to provide an unprotected -OH group for R¹. Suitable protecting groups are disclosed in Green et al., Protective Groups In Organic Synthesis, Second Edition, John Wiley & Sons Inc., New York, 1991, the disclosure of which is
5 incorporated herein by reference thereto.

For example, when R¹ is -OH suitable R³ groups include -OC(O)R⁴ (an ester) or -OC(O)OR⁵ (a carbonate). R⁴ is selected from C₁ to C₆ alkyl, -CF₃, -CCl₃, aryl (such as phenyl, benzyl or naphthyl), vinyl (-CH=CH₂) or allyl (CH₂=CHCH₂-). R⁵ is selected
10 from C₁ to C₆ alkyl, aryl (such as phenyl or benzyl), vinyl (-CH=CH₂) or allyl (CH₂=CHCH₂-). Preferably, R³ is -OC(O)OR⁵, more preferably R³ is -OC(O)OR⁵ wherein R⁵ is C₁ to C₆ alkyl, and most preferably R³ is -OC(O)OR⁵ wherein R⁵ is -C₂H₅.

The starting reactant of Formula 2.0, wherein R³ is H, Cl, or
15 -OC(O)R⁴, wherein R⁴ is C₁ to C₆ alkyl or -CF₃, and wherein R³ is -OC(O)OR⁵ wherein R⁵ is C₁ to C₆ alkyl, can be made according to the procedures disclosed in International Application No. PCT/US95/06600 filed on May 30, 1995, and U.S. Application Serial No. 08/252,302 filed on June 1, 1994, the disclosures of
20 each being incorporated herein by reference thereto.

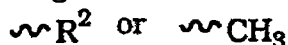
The starting reactant of Formula 2.0 wherein R³ is -OC(O)R⁴ and R⁴ is selected from -CCl₃, aryl (such as phenyl, benzyl or naphthyl), vinyl (-CH=CH₂) or allyl (CH₂=CHCH₂-), or wherein R³ is -OC(O)OR⁵ and R⁵ is selected from aryl (such as
25 phenyl or benzyl), vinyl or allyl, can be made by those skilled in the art using the appropriate reactants in accordance with procedures described in the above mentioned applications.

For example, when R⁴ is phenyl, benzyl, naphthyl, vinyl or allyl the reactants ClC(O)C₆H₅, ClC(O)CH₂C₆H₅, ClC(O)C₁₀H₇,
30 ClC(O)CH=CH₂, or ClC(O)CH₂CH=CH₂ can be used, respectively, to provide the desired -OC(O)R⁴ group. When R⁵ is phenyl, benzyl, vinyl or allyl the reactants ClC(O)OC₆H₅, ClC(O)OCH₂C₆H₅, ClC(O)OCH=CH₂, or ClC(O)OCH₂CH=CH₂ can be used, respectively, to provide the desired -OC(O)OR⁵ group. The
35 solvent for these reactions is, for example, methylene chloride in the presence of triethylamine.

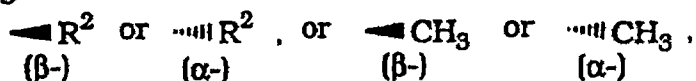
Those skilled in the art will appreciate that the bond

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represents the  $\alpha$  or  $\beta$  configuration. For example,



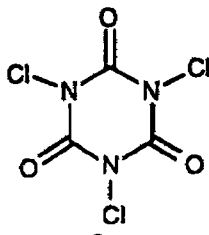
represents



5 respectively.

The reactions of the bromoformate (3.0) or the chloroformate (3.0A) to produce the epoxy steroid (1.0) are preferably conducted under an inert atmosphere, such as nitrogen.

10 The compound of Formula 2.0 is reacted with a suitable brominating reagent or chlorinating agent. Suitable brominating agents are DBH or NBS, with DBH being preferred. Suitable chlorinating agents are N-chloroimides or an N-chloroamides. Examples of chlorinating reagents include: N-chloroacetamide, 15 N-chlorosuccinimide, 1,3-dichloro-5,5-dimethylhydantoin, or 1,3,5-trichloroisocyanuric acid. Preferably, 1,3-dichloro-5,5-dimethylhydantoin or 1,3,5-trichloroisocyanuric acid is used. Most preferably, 1,3,5-trichloroisocyanuric acid, i.e.,



20 Preferably, a brominating reagent is used.

The reaction of the compound of Formula 2.0 with the brominating or chlorinating agent takes place in DMF, to which a catalytic amount of 70%  $HClO_4$  is added. A sufficient amount of the compound of Formula 2.0 and the brominating or chlorinating 25 agent are used to allow the reaction to proceed at a reasonable rate to obtain the desired bromoformate of Formula 3.0 or the desired chloroformate of 3.0A.

At least about 0.5 molar equivalents (Meq) of the brominating agent, such as DBH, or chlorinating agent is used. 30 Usually, about 0.5 to about 2.0 Meq are used, with about 0.65 to about 1.0 Meq being preferred, and about 0.7 to about 0.8 Meq being more preferred, and about 0.75 Meq being most preferred.

DMF is used in an excess relative to the compound of Formula 2.0. Enough DMF is used to function as a solvent and a reactant, and preferably, the minimum required amount is used. A volume of DMF is used which is in an excess of about 2 to 20  
5 times the amount of the compound of Formula 2.0, with about 2 to about 5 times being preferred, and about 3 to about 4 times being more preferred, and about 3.5 times being most preferred.

The 70%  $\text{HClO}_4$  is used in catalytic amounts, and preferably the minimum required amount is used. At least about 0.5 Meq of  
10 70%  $\text{HClO}_4$  is used, with suitable amounts being about 0.5 to about 3.0 Meq, and about 0.5 to about 1.0 Meq being preferred, and about 0.5 to about 0.7 Meq being more preferred, and about 0.6 Meq being most preferred.

The reaction of a compound of Formula 2.0 with the  
15 brominating agent or chlorinating is conducted at a temperature of about 0 to about 40°C, with about 5 to about 30°C being preferred, and about 10 to about 25°C being more preferred, and about 10 to about 20°C being most preferred.

Those skilled in the art will appreciate that the reaction  
20 forming the bromoformate or chloroformate can be monitored by known techniques to determine when the reaction is complete. For example, HPLC can be used to monitor the reaction to determine when all of the starting material has been used up.

Preferably, the bromoformate of Formula 3.0 or the  
25 chloroformate of 3.0A is isolated from the reaction mixture, by techniques well known in the art, before proceeding to the next reaction (epoxide formation). The bromoformate or chloroformate can be isolated as a wet cake by quenching the reaction in an excess of water to precipitate the bromoformate or  
30 chloroformate and then filtering the resulting slurry. Preferably, a  $\text{C}_1$  to  $\text{C}_6$  alkanol (e.g., methanol, ethanol, or isopropanol, with methanol being preferred) is added to the water that the reaction is quenched in.

For example, for quenching reactions of compounds  
35 wherein  $\text{R}^2$  is in the  $\beta$ -position, alkanol (e.g., methanol) is used in an amount that is at least about 3.5 times (3.5X) the amount of the compound of Formula 2.0, with about 3.5X being preferred. Preferably, the quenching solution (water and alkanol mixture) is

at least about 5% alkanol, preferably methanol, with about 5 to about 25% being preferred, and about 10 to about 15% being more preferred, and about 12 to about 14% being still more preferred, and about 13% being most preferred.

- 5       Also, for example, for quenching reactions of compounds wherein  $R^2$  is in the  $\alpha$ -position, alkanol (e.g., methanol) is used in an amount that is at least about 13 times (13X) the amount of the compound of Formula 2.0, with about 13X being preferred. Preferably, the quenching solution (water and alkanol mixture) is  
10       about 5 to about 30% alkanol (preferably methanol), with about 10 to about 20% being preferred, and about 10 to about 15% being more preferred, and about 14% being most preferred.

- To produce the epoxy steroid of Formula 1.0, the bromoformate of Formula 3.0 or chloroformate of 3.0A is reacted  
15       with a strong base in an organic solvent mixture comprising: (a) THF or  $CH_2Cl_2$  and (b) a  $C_1$  to  $C_6$  alkanol or acetonitrile.

- Suitable strong bases are those bases which provide  $-OH$  ions upon dissociation in aqueous solution. The strong base can be an inorganic base, such as NaOH or KOH; or an organic base,  
20       such as sodium methoxide, potassium methoxide, sodium butoxide, potassium butoxide, sodium t-butoxide or potassium t-butoxide. Preferably, NaOH is used.

- A sufficient amount of water is used to dissolve the base and provide  $-OH$  ions in solution. The base is added as an aqueous  
25       solution to the reaction mixture, or the base can be added to the reaction mixture to which a sufficient amount of water is added to dissolve the base. Preferably, the base is added as a freshly prepared aqueous solution.

- At least about 7.5 Meq of water is used to provide an  
30       aqueous solution of the base, and suitably about 7.5 to about 50 Meq of water are used, with about 7.5 to about 25 being preferred, and about 10 to about 20 Meq being more preferred, and about 14 to about 16 Meq being even more preferred, and about 15 Meq of water being most preferred.

- 35       The base is used in an amount which effectively causes formation of the 9,11 $\beta$ -epoxide, and when present, hydrolysis of the  $R^3$  ester or carbonate protecting groups to an  $R^1 -OH$  group.

When  $R^3$  is selected from H or Cl, the base, such as NaOH, is used in amounts of about 1.0 to about 4.0 Meq, with about 1.5 to about 2.0 Meq being preferred.

When  $R^3$  is an ester or carbonate protecting group, such as  
5 -OC(O) $R^4$  or -OC(O) $OR^5$ , then the base, such as NaOH, is used in amounts of about 2.0 to about 4.0 Meq, with about 2.5 to about 3.5 Meq being preferred, and about 3.0 Meq being most preferred.

For the organic solvent mixture used in the epoxide reaction,  $CH_2Cl_2$  is preferably used for compounds wherein  $R^2$  is  
10 in the  $\alpha$ - or  $\beta$ - position. When THF is used it is more preferably used with compounds wherein  $R^2$  is in the  $\alpha$ - position.

Examples of  $C_1$  to  $C_6$  alkanols include but are not limited to: methanol, ethanol or isopropanol. Preferably, methanol is used with the THF or  $CH_2Cl_2$ .

15 The  $CH_2Cl_2$  or THF, preferably  $CH_2Cl_2$ , is used as a solvent in an excess relative to the amount of the compound of Formula 2.0. Usually, the solvent is used in an excess of at least about 3 times (3X) the amount of the compound of Formula 2.0, with  
20 suitable amounts being about 3X to about 20X, and about 4X to about 10X being preferred, and about 5X to about 8X being more preferred, and about 6X to about 7X being most preferred.

The  $C_1$  to  $C_6$  alkanol or acetonitrile, preferably methanol, is used in an excess relative to the amount of the compound of Formula 2.0. Usually, when  $R^2$  is in the  $\alpha$ -position, the alkanol or  
25 acetonitrile is used in an excess of at least about one time (1X) the amount of the compound of Formula 2.0, with suitable amounts being about 1X to about 20X, and about 1X to about 5X being preferred, and about 1X to about 3X being more preferred, and about 2X being most preferred.

30 When  $R^2$  is in the  $\beta$ -position, the alkanol or acetonitrile is used in an excess of at least about three times (3X) the amount of the compound of Formula 2.0, with suitable amounts being about 3X to about 20X, and about 3X to about 10X being preferred, and about 5X to about 7X being more preferred, and about 6X being  
35 most preferred.

The reaction of the bromoformate of Formula 3.0 or the chloroformate of Formula 3.0A with base to form the epoxide of Formula 1.0 is conducted at a temperature low enough to reduce

the formation of unwanted by-products. Generally, a temperature of about +10 to about -20°C is used, with about 0 to about -10°C being preferred, and about -2 to about -6°C being more preferred, and about -5°C being most preferred.

5        Those skilled in the art will appreciate that the reaction to form the epoxide can be monitored by known techniques, such as HPLC, to determine when the reaction is complete--i.e., to determine when no more starting reactant is present. The reaction can then be quenched, with an organic acid, to a pH of  
10        about 3 to about 5. Suitable organic acids include but are not limited to acetic acid, formic acid, and tartaric acid, with acetic acid being preferred.

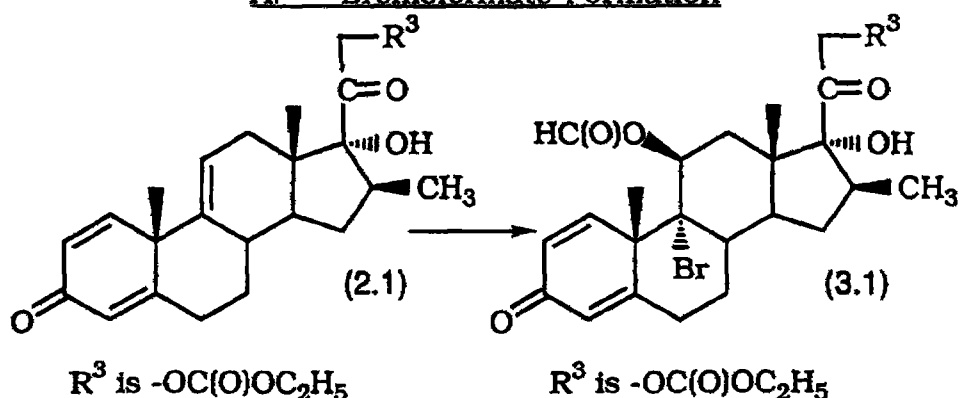
15        The epoxy steroid of Formula 1.0 can be isolated by known techniques. Since the epoxy steroid is normally obtained as a precipitate, it can be isolated by filtration.

20        The epoxide can be purified by techniques well known in the art. For example, in a preferred purification method the epoxide of Formula 1.0 is dissolved by heating in a sufficient amount of a mixture of CH<sub>2</sub>Cl<sub>2</sub> and methanol. The resulting  
mixture is then filtered, concentrated, cooled, filtered, washed (preferably with methanol), and dried under vacuum to yield the purified epoxide of Formula 1.0.

25        The epoxy steroid obtained can be utilized to produce other known steroids using known techniques. For example, the epoxy steroid can be used to produce Betamethasone, Beclomethasone, Dexamethasone or Mometasone Furoate.

30        The examples that follow are intended to exemplify the claimed invention, and such examples should not be construed as limiting the disclosure or the claimed invention.

The water used in the examples was deionized water.

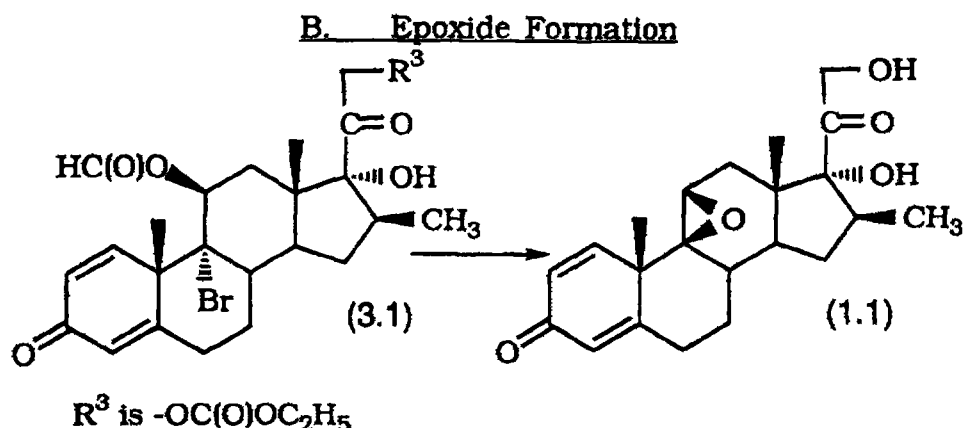
EXAMPLE 1A. Bromoformate Formation

5 The 16 $\beta$ -methyl-triene-21-cathylate of Formula 2.1 (about 90% pure) (50 g) was dissolved in DMF (175 ml) at room temperature. This mixture was cooled to about 10°C, and then 70% HClO<sub>4</sub> (6.25 ml) was added to the mixture. This addition was done during a five minute time period to keep the reaction temperature below 20°C. The mixture was cooled to about 10°C and DBH (25.1 g) was added to the mixture. This addition was done over about a 15 minute time period to keep the reaction temperature below 20°C.

15 After about 3 hours HPLC indicated that some starting material was still present so an additional 0.5 g of DBH was added and agitation was continued for about one hour. When HPLC indicated that the reaction was complete, the reaction mixture was diluted with CH<sub>3</sub>OH (175 ml) and agitated for about 10 minutes. The bromoformate of Formula 3.1 was precipitated in 1500 ml of water at room temperature. This mixture was agitated at room temperature for about 40 minutes, and then ice (700 g) was added to bring the temperature to <10°C. The mixture was agitated at <10°C for about 30 minutes and then filtered and the precipitate (wet cake) was washed with water (about 1000 ml). The wet cake was dried overnight under vacuum to yield a wet cake of about 114 g.

25 An analytical sample of the wet cake was taken and dried under vacuum for NMR analysis. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): 8.12 (s, 1H), 6.85 (d, J=10 Hz, 1H), 6.34 (dd, J=10, 1.7 Hz, 1H), 6.10 (d, 1.6 Hz, 1H), 5.90 (br s, 1H), 5.02 (d, J=18 Hz, 1H), 4.86 (d, J=18 Hz, 1H), 4.22 (q, J=7 Hz, 2H), 2.89 (dd, J=14.8, 3.6 Hz,

1H), 2.60 (m, 1H), 2.40 (m, 2H), 2.15 (m, 3H), 1.95 (m, 1H),  
 1.75 (m, 2H), 1.58 (s, 3H), 1.33 (t, J=7 Hz, 3H), 1.25 (m, 1H),  
 1.19 (d, J=7 Hz, 3H), and 1.00 (s, 3H). <sup>13</sup>C-NMR (100.6 MHz,  
 CDCl<sub>3</sub>): 204.8, 186.3, 165.4, 159.6, 155.2, 151.5, 130.1, 125.6,  
 5 89.2, 82.2, 75.1, 72.0, 64.9, 49.8, 49.7, 49.5, 44.6, 35.9, 34.5,  
 33.8, 31.0, 29.1, 25.1, 20.1, 17.9, and 14.6.



10 The bromoformate wet cake (113 g) from Step A was  
 dissolved in a mixture of CH<sub>2</sub>Cl<sub>2</sub> (350 ml) and methanol (325 ml).  
 The resulting mixture was cooled to about -5°C, vacuum degased  
 three times under nitrogen, and kept under nitrogen. A NaOH  
 solution was made by dissolving NaOH (15 g) in water (15 ml),  
 15 and the resulting NaOH solution was cooled to about 5°C. The  
 freshly prepared NaOH solution was added to the bromoformate-  
 CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH mixture. The addition of the NaOH solution was  
 done slowly over about a one hour time period (0.3ml/minute)  
 while keeping the temperature of the reaction mixture between  
 20 about -5 and about -3°C.

The resulting reaction mixture was agitated at about -3 to  
 about -5°C for about two hours. After HPLC indicated the reaction  
 was complete, the reaction mixture was quenched with acetic  
 acid (40 ml). The reaction mixture was concentrated to 250 ml  
 25 by distillation of the CH<sub>2</sub>Cl<sub>2</sub> and vacuum distillation of the CH<sub>3</sub>OH.  
 Then water (175 ml) was added to the mixture and this mixture  
 was concentrated to 250 ml. This was followed by addition of  
 water (500 ml) and cooling to about 1°C of the resulting slurry.  
 The slurry was agitated for about 30 minutes at about 1°C and  
 30 then filtered and the wet cake obtained was washed with water.

The wet cake was dried under vacuum at about 50°C for about 16 hours to provide 41.2 g (purity 90.0% against a standard) of the crude epoxide (Formula 1.1). This represents a 97% molar yield from the triene-21-cathylate (Formula 2.1).

5 The crude epoxide (Formula 1.1) (41.1g) was heated in a mixture of CH<sub>2</sub>Cl<sub>2</sub> (697 ml) and methanol (205 ml) until dissolved. The resulting solution was filtered and concentrated to a volume of about 164 ml. The resulting slurry was cooled to about 1°C, agitated for about 30 minutes at about 1°C, filtered, and  
10 washed with cold methanol (2 X 25 ml). The resulting wet cake was dried under vacuum at about 50°C to provide 36.0 g of the epoxide (Formula 1.1) with a purity of 99% against a standard. This represents a 96% recovery and 93% overall molar yield from the triene-21-cathylate (Formula 2.1).

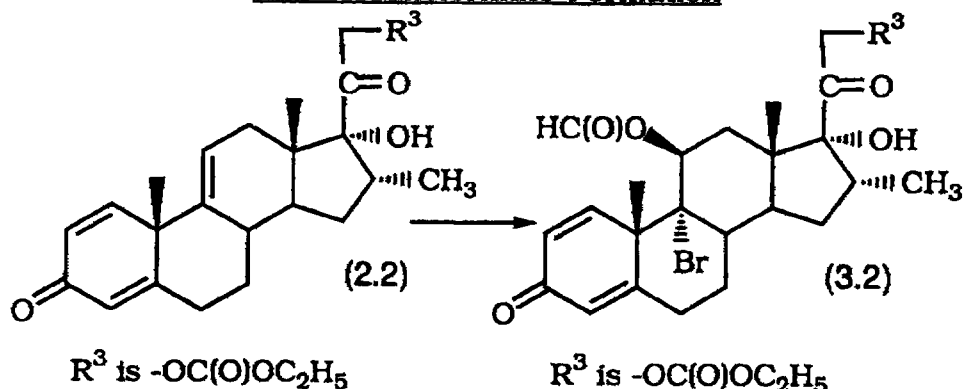
15 HPLC retention time and <sup>1</sup>H-NMR of the epoxide are identical to those of a reference compound.

<sup>1</sup>H-NMR (400 MHz), DMSO): 6.62 (d, J=10 Hz, 1H), 6.10 (br s, 1H), 6.09 (dd, J=10, 1.8 Hz, 1H), 5.26 (s, 1H), 4.52 (t, J=5.8 Hz, 1H), 4.37 (dd, J=19.4, 5.9 Hz, 1H), 4.10 (dd, J=19.3, 5.8 Hz, 1H), 3.19 (br s, 1H), 2.67 (m, 1H), 2.45 (m, 2H), 2.36 (m, 2H), 2.21 (m, 2H), 2.05 (m, 2H), 1.59 (m, 1H), 1.52 (m, 1H),  
20 1.37 (s, 3H), 1.33 (m, 1H), 1.01 (d, J=6.6 Hz, 3H), 0.86 (s, 3H).

## EXAMPLE 2

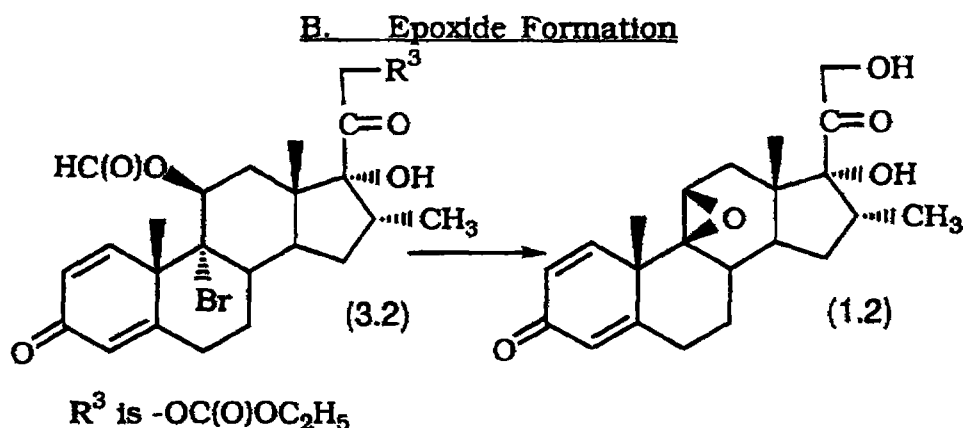
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### A. Bromoformate Formation



The 16 $\alpha$ -methyl-triene-21-cathylate of Formula 2.2 (about 86% pure) (10 g) was dissolved in DMF (50 ml) at room temperature. Then 70% HClO<sub>4</sub> (1.25 ml) was added to the  
30 mixture. Next, DBH (4.5 g) was added at room temperature over

about a 15 minute time period. The resulting mixture was agitated at room temperature for about one hour and monitored by HPLC. When HPLC indicated that the reaction was not complete, about 0.2 g of DBH was added, and agitation was continued for about 30 minutes. When HPLC indicated the reaction was complete, CH<sub>3</sub>OH (100 ml) was added to the mixture. The bromoformate of Formula 3.2 was precipitated in water (1000 ml) containing CH<sub>3</sub>OH (100 ml). The mixture was filtered and the wet cake of bromoformate was washed with water.



The wet cake of bromoformate from Step A was dissolved in a mixture of THF (80 ml) and CH<sub>3</sub>OH (80 ml). The resulting solution is vacuum degassed under nitrogen, kept under a nitrogen atmosphere and cooled to about -3°C. A NaOH solution was prepared by dissolving NaOH (1.75 g) in water (7.5 ml) and then cooling the resulting NaOH solution to about 0 to about 5°C. The NaOH solution was added to the bromoformate-THF/CH<sub>3</sub>OH solution over about a one hour time period while keeping the temperature of the reaction mixture between about -4.0 and about -2.0°C. When HPLC indicated that the reaction was not complete after about 2 hours of agitation at about -3°C (about 17% starting material left), additional NaOH solution (0.6 g NaOH in 3 ml of water) was added to the reaction mixture over about a 15 minute time period.

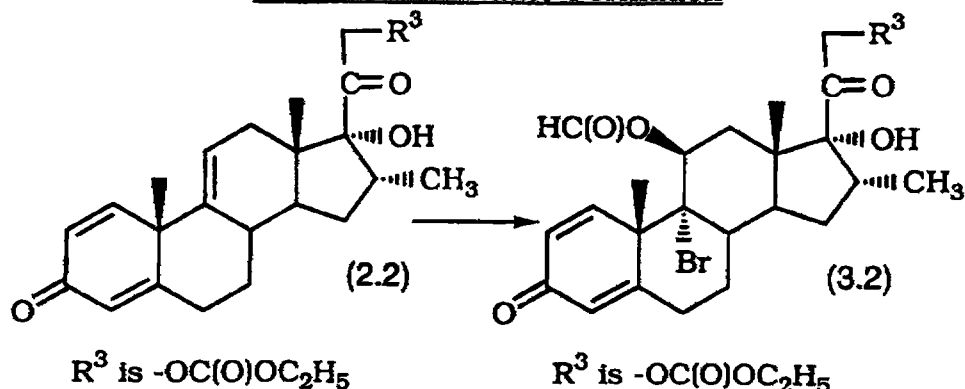
When HPLC indicated the reaction was complete (about 30 minutes), the reaction was quenched with a solution of acetic acid (4 ml) in water (4 ml). The solvents were removed by

distillation to concentrate the mixture, and during distillation water was added in order to remove the residual solvent. The volume was then brought to about 150 ml with water. The mixture was cooled to about 0 to about 5°C and agitated for about 30 minutes. The mixture was then filtered and the wet cake was washed with water. The wet cake was dried under vacuum at about 60°C to yield 8.06 g of crude epoxide (Formula 1.2) that was 86.7% pure.

The crude epoxide (8.05 g) was dissolved by refluxing in a solution of CH<sub>3</sub>OH (60 ml) and CH<sub>2</sub>Cl<sub>2</sub> (40 ml). The mixture was agitated for about 30 minutes and then concentrated to about 40 ml (45 ml of solvent was collected). The solution was slowly cooled to room temperature and then cooled to about 0 to about 5°C. The mixture was filtered, the precipitate was washed with cold CH<sub>3</sub>OH (2 X 6 ml), and dried under vacuum. The epoxide of Formula 1.2 was obtained as white crystals, 6.6 g, having a purity of 99% and an overall molar yield of 87% (based on the starting triene-21-cathylate of Formula 2.2). <sup>1</sup>H-NMR (400 MHz, DMSO): 6.47 (d, J=10 Hz, 1H), 5.96 (br s, 1H), 5.93 (dd, J=10, 1.7 Hz, 1H), 4.89 (s, 1H), 4.54 (t, J=5.9 Hz, 1H), 4.31 (dd, J=19.3, 6.4 Hz, 1H), 3.88 (dd, J=19.3, 6.4 Hz, 1H), 3.05 (br s, 1H), 2.74 (m, 1H), 2.51 (m, 1H), 2.32 (m, 1H), 2.10 (m, 3H), 1.61 (m, 1H), 1.47 (m, 1H), 1.34 (m, 1H), 1.22 (s, 3H), 1.14 (m, 1H), 1.05 (m, 1H), 0.60 (d, J=6.8 Hz, 3H), 0.59 (s, 3H).

### EXAMPLE 3

#### A. Bromoformate Formation



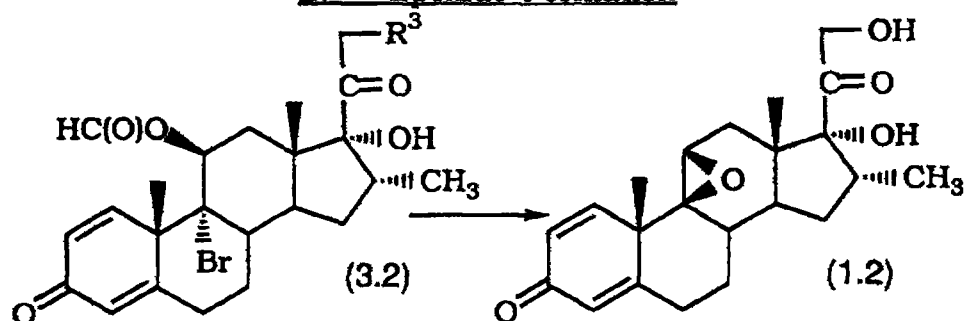
The 16 $\alpha$ -methyl-triene-21-cathylate of Formula 2.2 (86.9% pure) (50 g) was suspended in DMF (175 ml) at room

temperature. Then 70%  $\text{HClO}_4$  (6.5 ml) was added at room temperature to the mixture. Next, DBH (25 g) was added at room temperature over about a 10 minute time period. The resulting mixture was agitated at room temperature until HPLC indicated  
 5 that the reaction was complete (about one hour).

Then the reaction mixture was diluted with  $\text{CH}_3\text{OH}$  (150 ml). The bromoformate of Formula 3.2 was precipitated, over about a 40 minute time period, in water (4000 ml) that contained  $\text{CH}_3\text{OH}$  (500 ml) and  $\text{Na}_2\text{SO}_3$  (6 g). The resulting mixture was  
 10 agitated at room temperature for about 30 minutes and then cooled to about  $4^\circ\text{C}$  and agitated at this temperature for about 30 minutes. The bromoformate was collected as a wet cake by filtration, and the wet cake was washed with water (2000 ml).

15

#### B. Epoxide Formation



The bromoformate from Step A was dissolved in a mixture of  $\text{CH}_2\text{Cl}_2$  (300 ml) and  $\text{CH}_3\text{OH}$  (25 ml). The aqueous layer was separated from the organic layer, and the aqueous layer was  
 20 extracted with  $\text{CH}_2\text{Cl}_2$  (100 ml). The organic layers were combined and  $\text{CH}_3\text{OH}$  (100 ml) was added to the resulting organic solution. The resulting solution was cooled to about  $-4^\circ\text{C}$ , vacuum degassed four times under nitrogen, and kept under nitrogen.

25 A NaOH solution was prepared by dissolving NaOH (15 g) in water (30 ml). The NaOH solution was cooled and was added to the bromoformate- $\text{CH}_2\text{Cl}_2$ / $\text{CH}_3\text{OH}$  solution over about a one hour time period while keeping the temperature of the reaction mixture below  $-2^\circ\text{C}$ . The reaction mixture was agitated at about

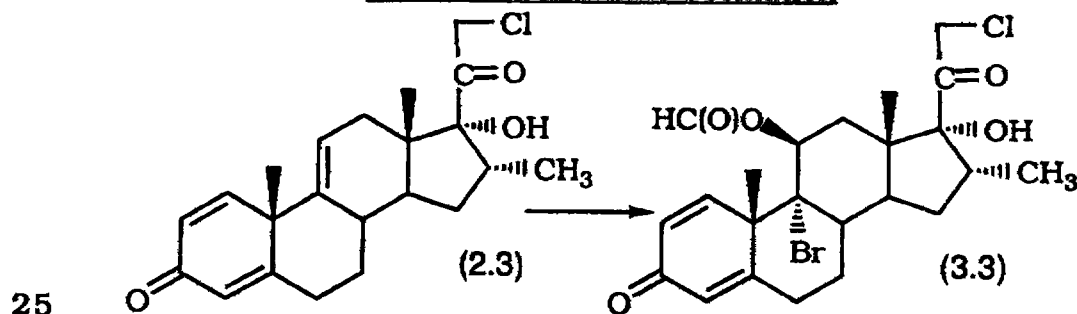
-4°C until HPLC indicated that the reaction was complete (about one hour).

Then the reaction was quenched with a mixture of acetic acid (10 ml) and water (10 ml). Water (125 ml) was added and the mixture was agitated for about 5 minutes. The aqueous and organic layers were separated, and the aqueous layer was extracted twice with CH<sub>2</sub>Cl<sub>2</sub> (125 ml). The organic layers were combined and CH<sub>3</sub>OH (200 ml) was added. The mixture was distilled to remove 250 ml of solvent. The mixture was then filtered and the residue was washed with CH<sub>2</sub>Cl<sub>2</sub> (about 50 ml) which was then added to the mixture being concentrated. The resulting organic solution was concentrated to a volume of 150 ml. The slurry obtained was cooled to about -2°C and agitated at this temperature for about 30 minutes, filtered, washed with cold CH<sub>3</sub>OH (30 ml), and then washed with a mixture (30 ml) of CH<sub>3</sub>OH and water (1:1). The precipitate was dried under vacuum at about 60°C to yield 35.5 g of epoxide (Formula 1.2) that had a purity of 99.2%, and a 93.3% overall molar yield from the triene of Formula 2.2.

The HPLC retention time and <sup>1</sup>H-NMR spectrum are identical with those of a reference compound.

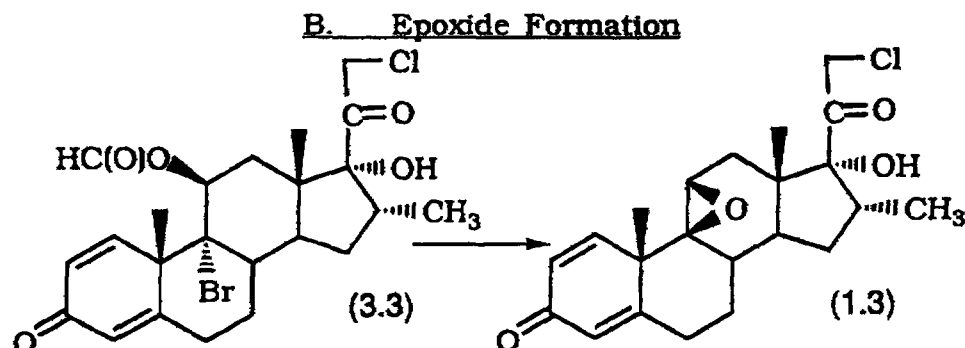
#### EXAMPLE 4

##### A. Bromoformate Formation



The triene chloride (1 g) of Formula 2.3 was dissolved in DMF (3.5 ml), and the resulting solution was cooled to about 13°C. 70% Perchloric acid (0.13 ml) was added to the solution followed by the addition of DBH (0.7 g). The mixture was agitated at room temperature until HPLC indicated the reaction was complete (about 2 hours).

Then CH<sub>3</sub>OH (3.5 ml) was added to the reaction mixture, and the resulting mixture was agitated for about 5 minutes. This resulted in the bromoformate of Formula 3.3 crystallizing out of solution. Next water (70 ml) containing CH<sub>3</sub>OH (7 ml) was added and the resulting mixture was agitated for about 30 minutes. The mixture was then filtered and the precipitate (wet cake) was washed with water. The wet cake was dried to provide 1.26 g of the bromoformate of Formula 3.3 with a purity of about 97% (by HPLC). <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): 8.13 (s, 1H), 6.80 (d, J=10 Hz, 1H), 6.36 (dd, J=10, 1.8 Hz, 1H), 6.11 (br s, 1H), 5.92 (br s, 1H), 4.59 (d, J=16 Hz, 1H), 4.23 (d, J=16 Hz, 1H), 3.20 (m, 1H), 2.51 (m, 4H), 2.17 (m, 1H), 1.85 (m, 2H), 1.72 (m, 2H), 1.58 (s, 3H), 1.30 (m, 1H), 0.98 (d, J=7 Hz, 3H), 0.96 (s, 3H). <sup>13</sup>C-NMR (100.6 MHz, CDCl<sub>3</sub>): 202.9, 185.9, 164.6, 159.3, 150.8, 130.0, 125.5, 91.2, 81.7, 74.7, 49.5, 48.8, 48.2, 44.9, 36.1, 36.0, 33.4, 31.8, 30.7, 28.6, 24.9, 17.8, and 14.8.



The bromoformate (1 g) from Step A was dissolved in a mixture of CH<sub>2</sub>Cl<sub>2</sub> (10 ml) and CH<sub>3</sub>OH (5 ml). The solution was cooled to about -5°C, degassed four times under vacuum and kept under nitrogen. A NaOH solution was prepared by dissolving NaOH (0.2 g) in water (1 ml). The NaOH solution was added slowly over about a 30 minute time period to the bromoformate-CH<sub>2</sub>Cl<sub>2</sub>/CH<sub>3</sub>OH solution to keep the reaction mixture at a temperature of about -5 to about -3°C. The reaction was monitored for completion (about one hour) by HPLC. The reaction was quenched with acetic acid (0.5 ml).

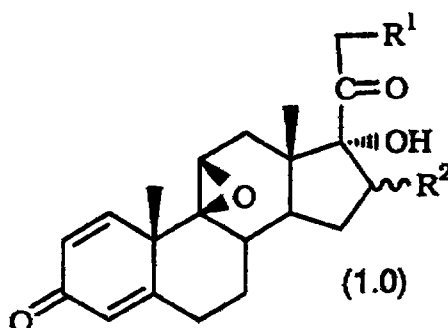
Next CH<sub>2</sub>Cl<sub>2</sub> (5 ml) and water (5 ml) were added to the mixture and the organic and aqueous layers were separated. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (5 ml), the organic

- layers were combined, and then washed with water (10 ml). The organic layer was concentrated to dryness to provide the epoxide (0.70 g) of Formula 1.3. The epoxide was 97% pure (by HPLC area) and the overall molar yield from the triene chloride
- 5 (Formula 2.3) was about 93%. <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): 6.61 (d, J=10 Hz, 1H), 6.22 (dd, J=10, 1.8 Hz, 1H), 6.17 (br s, 1H), 4.58 (d, J=16 Hz, 1H), 4.21 (d, J=16 Hz, 1H), 3.05 (m, 1H), 2.60 (m, 1H), 2.45 (m, 1H), 2.28 (m, 2H), 2.19 (m, 1H), 1.60 (m, 4H), 1.37 (s, 3H), 1.28 (m, 1H), 0.86 (s, 3H), 0.92 (d, J=7 Hz, 3H).
- 10 The HPLC retention time and <sup>1</sup>H-NMR spectrum of the epoxide are identical with those of a reference standard.

- While the present invention has been described in conjunction with the specific embodiments set forth above, many
- 15 alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

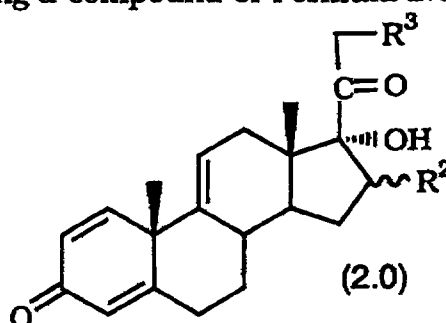
WHAT IS CLAIMED IS:

1. A process for producing an epoxy steroid of Formula 1.0:

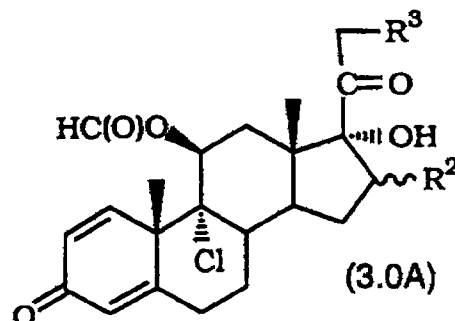
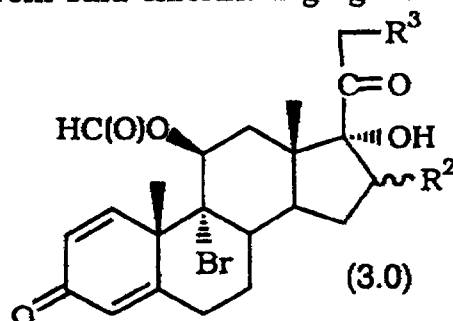


wherein  $R^1$  is selected from H, -OH, or Cl; and  $R^2$  is selected from hydrogen or lower alkyl; said process comprising:

- (A) reacting a compound of Formula 2.0:



- with a brominating agent selected from DBH or NBS, or a chlorinating agent selected from an N-chloroimide or N-chloroamide, said reaction being conducted in DMF containing a catalytic amount of 70%  $\text{HClO}_4$ , at a temperature of about 0 to about  $+40^\circ\text{C}$ , thereby producing the bromoformate of Formula 3.0 from said brominating agent or the chloroformate of Formula 3.0A from said chlorinating agent:



wherein:  $R^2$  is as defined above; and when  $R^1$  is H then  $R^3$  is H; and when  $R^1$  is -OH then  $R^3$  is a suitably protected -OH group; and when  $R^1$  is Cl then  $R^3$  is Cl; and



- (B) reacting, at a temperature of about -20 to about +10°C, the bromoformate of Formula 3.0 or the chloroformate of Formula 3.0A with a strong base in an organic solvent mixture comprising: (a) THF or CH<sub>2</sub>Cl<sub>2</sub> and (b) a C<sub>1</sub> to C<sub>6</sub> alkanol or acetonitrile; thereby producing the epoxy steroid of Formula 1.0.
2. The process of Claim 1 wherein when R<sup>1</sup> is -OH then R<sup>3</sup> is -OC(O)OR<sup>5</sup> wherein R<sup>5</sup> is a C<sub>1</sub> to C<sub>6</sub> alkyl group.
3. The process of Claim 1 wherein R<sup>3</sup> is -OC(O)OC<sub>2</sub>H<sub>5</sub>.
4. The process of Claim 1 wherein said brominating agent is used and said brominating agent is DBH, and the reaction forming the bromoformate is conducted at a temperature of about +10 to about +20°C.
5. The process of Claim 1 wherein the strong base is selected from NaOH or KOH.
6. The process of Claim 1 wherein the strong base is NaOH.
7. The process of Claim 1 wherein said organic solvent mixture in Step (B) is a mixture of CH<sub>2</sub>Cl<sub>2</sub> and CH<sub>3</sub>OH.
8. The process of Claim 1 wherein the reaction in Step (B) is conducted at a temperature of about 0 to about -10°C.
9. The process of Claim 1 wherein R<sup>3</sup> is Cl.
10. The process of Claim 1 wherein: (1) when R<sup>1</sup> is -OH then R<sup>3</sup> is -OC(O)OR<sup>5</sup> wherein R<sup>5</sup> is a C<sub>1</sub> to C<sub>6</sub> alkyl group; (2) in Step (A) said brominating agent is used and said brominating agent is DBH and the reaction forming the bromoformate is conducted at a temperature of about +10 to about +25°C; and (3) in Step (B) the strong base is selected from NaOH or KOH, said organic solvent mixture is a mixture of CH<sub>2</sub>Cl<sub>2</sub> and methanol, and



the reaction forming the epoxide is conducted at a temperature of about 0 to about -10°C.

11. The process of Claim 10 wherein when R<sup>1</sup> is -OH  
5 then R<sup>3</sup> is -OC(O)OC<sub>2</sub>H<sub>5</sub> and said base is in Step (B) is NaOH.

12. The process of Claim 11 wherein R<sup>2</sup> is methyl.

13. The process of Claim 12 wherein the brominating  
10 agent is used in amounts of about 0.5 to about 2.0 Meq, the 70% HClO<sub>4</sub> is used in amounts of about 0.5 to about 3.0 Meq, the base is used in amounts of about 1.0 to about 4.0 Meq when R<sup>3</sup> is H or Cl, and when R<sup>3</sup> is -OC(O)OC<sub>2</sub>H<sub>5</sub> the base is used in amounts of about 2.5 to about 3.5 Meq.

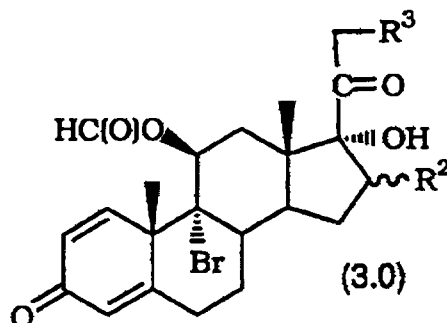
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14. The process of Claim 13 wherein R<sup>1</sup> is -OH or -Cl.

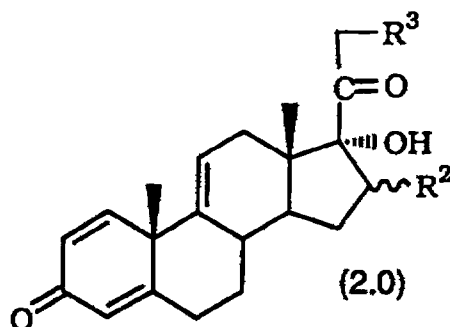
15. The process of Claim 14 wherein the reaction in Step  
(A) is conducted at a temperature of about +10 to about +20°C,  
20 and the reaction in Step (B) is conducted at a temperature of about -2 to about -6°C.

16. The process of Claim 15 wherein R<sup>1</sup> is -OH.

25 17. A process for producing a bromoformate of Formula 3.0:



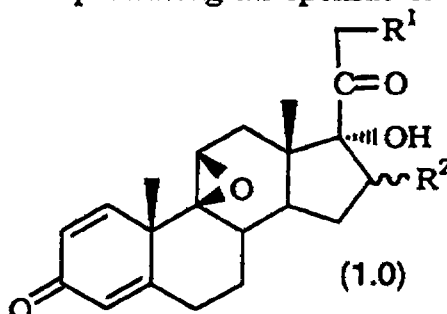
comprising reacting a compound of Formula 2.0:



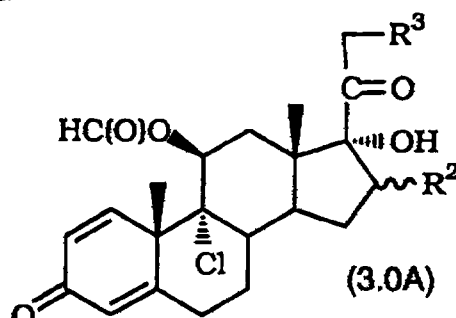
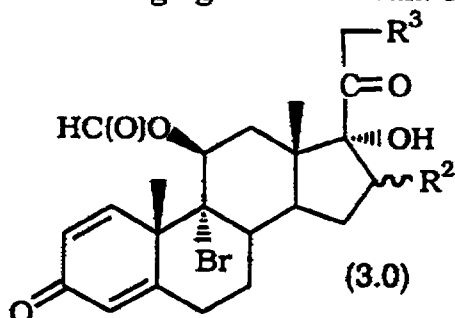
with a brominating agent selected from DBH or NBS, in DMF containing a catalytic amount of 70%  $\text{HClO}_4$ , at a temperature of about 0 to about  $+40^\circ\text{C}$ ; wherein  $\text{R}^2$  is selected from hydrogen or lower alkyl; and  $\text{R}^3$  is selected from H, a  $-\text{OH}$  protecting group, or Cl.

18. The process of Claim 17 wherein said brominating agent is DBH, said reaction is conducted at a temperature of about  $+10$  to about  $+20^\circ\text{C}$ ,  $\text{R}^2$  is methyl, and  $\text{R}^3$  is  $-\text{OC}(\text{O})\text{OC}_2\text{H}_5$  or Cl.

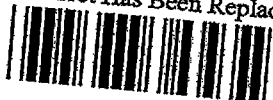
19. A process for producing an epoxide of Formula 1.0:



comprising reacting a bromoformate of Formula 3.0 or a chlorinating agent of Formula 3.0A:



with a strong base in an organic solvent mixture comprising: (a) THF or  $\text{CH}_2\text{Cl}_2$  and (b) a  $\text{C}_1$  to  $\text{C}_6$  alkanol or acetonitrile, at a temperature of about  $-20$  to about  $+10^\circ\text{C}$ ; wherein:  $\text{R}^1$  is selected





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from H, -OH, or Cl;  $R^2$  is selected from hydrogen or lower alkyl; and  $R^3$  is selected from H when  $R^1$  is H, a suitably protected -OH group when  $R^1$  is -OH, or Cl when  $R^1$  is Cl.

- 5            20. The process of Claim 19 wherein said base is NaOH, and said organic solvent mixture is a mixture of  $CH_2Cl_2$  and methanol, said reaction is conducted at a temperature of about -2 to about  $-6^\circ C$ , and  $R^3$  is  $-OC(O)OC_2H_5$  or Cl.