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<th><strong>Title</strong></th>
<th>Method for synthesizing 5beta, 6beta-epoxides of steroids by a highly beta-selective epoxidation of delta5-unsaturated steroids catalyzed by ketones</th>
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<td><strong>Inventor(s)</strong></td>
<td>Yang, D; Jiao Guan-Sheng</td>
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METHOD FOR SYNTHESIZING 5BETA, 6BETA-EPOXIDES OF STEROIDS BY A HIGHLY BETA-SELECTIVE EPOXIDATION OF DELTA5-UNSATURATED STEROIDS CATALYZED BY KETONES

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ABSTRACT
A general, efficient, and environmentally friendly method is provided for producing mostly β-epoxides of Δ5-unsaturated steroids using certain ketones as the catalyst along with an oxidizing agent, or by using certain dioxiranes. In another aspect of the invention, a method is provided for producing mostly 5β,6β-epoxides of steroids from Δ5-unsaturated steroids having a substituent at the 3α-position by an epoxidation reaction using a ketone along with an oxidizing agent under conditions effective to generate epoxides, or using a dioxirane under conditions effective to generate epoxides. A whole range of Δ5-unsaturated steroids, bearing different functional groups such as hydroxy, carbonyl, acetyl or ketal group as well as different side chains, were conveniently converted to the corresponding synthetically and biologically interesting 5β,6β-epoxides with excellent β-selectivities and high yields.
KETONES:

STEROIDS:

Fig. 2
**Fig. 3**

\[
\text{KETONE OXONE/NaHCO}_3 \xrightarrow{\text{DMM/CH}_3\text{CN/H}_2\text{O}} \text{rt, pH 7.0 - 7.5}
\]

**5a-20a (α-EPOXIDE)**

**5b-20b (β-EPOXIDE)**

**Fig. 4**

TABLE 1, ENTRY 4

![Chemical diagram with spectra and ppm values](image-url)
Fig. 5

AUTHENTIC_SAMPLES_OF_5a/5b

Fig. 6

TABLE_1, ENTRY_1
Fig. 7

TABLE 1, ENTRY 2

Fig. 8

TABLE 1, ENTRY 3
Fig. 13

TABLE 1, ENTRY 6

Fig. 14

AUTHENTIC SAMPLES OF 7a/7b
**Fig. 19**

TABLE 1, ENTRY 8

**Fig. 20**

AUTHENTIC SAMPLES OF 9a/9b
Fig. 21

TABLE 1, ENTRY 8

Fig. 22

TABLE 1, ENTRY 9

(10 mmol scale)
Fig. 23

TABLE 1, ENTRY 10

Fig. 24

AUTHENTIC SAMPLES
OF 10a/10b
Fig. 25

TABLE 1, ENER 10

Fig. 26

TABLE 2, ENTRY 2
Fig. 27

AUTHENTIC SAMPLES OF 11a/11b

Fig. 28

TABLE 2, ENTRY 1

PPM: 3.2 3.1 3.0 2.9 2.8 2.7
Fig. 33

AUTHENTIC SAMPLES
OF 12a/12b

Fig. 34

TABLE 2, ENTRY 5

PPM

3.2  3.1  3.0  2.9  2.8  2.7

18000

10000

72003

1000

PPM

3.1  3.0  2.9  2.8  2.7  2.6
Fig. 39

TABLE 2, ENTRY 8

Fig. 40

TABLE 2, ENTRY 9
Fig. 41

TABLE 2, ENTRY 10

Fig. 42

14b

TABLE 2, ENTRY 11
Fig. 43

AUTHENTIC SAMPLES OF 14a/14b

Fig. 44

TABLE 2, ENTRY 11
Fig. 51

AUTHENTIC SAMPLES
OF 16a/16b

Fig. 52

TABLE 2, ENTRY 15
Fig. 53

TABLE 2, ENTRY 16

Fig. 54

TABLE 2, ENTRY 17
Fig. 55

AUTHENTIC SAMPLES OF 17a/17b

PPM 3.2 3.1 3.0 2.9 2.8 2.7

Fig. 56

TABLE 2, ENTRY 17

PPM 3.2 3.1 3.0 2.9 2.8 2.7

Fig. 57

TABLE 2, ENTRY 18

PPM 3.2 3.1 3.0 2.9 2.8 2.7
Table 2, Entry 19

Fig. 58

Fig. 59

Authentic samples of 18a/18b
**Fig. 64**

AUTHENTIC SAMPLES OF 19a/19b

**Fig. 65**

TABLE 2, ENTRY 21
Fig. 68

AUTHENTIC SAMPLES
OF 20a/20b

Fig. 69

TABLE 2, ENTRY 23

Fig. 70

TABLE 2, ENTRY 24
METHOD FOR SYNTHESIZING 5BETA,
6BETA-EPOXIDES OF STEROIDS BY A HIGHLY
BETA-SELECTIVE EPOXIDATION OF
DELTA5-UNSATURATED STEROIDS CATALYZED
BY KETONES

[0001] This application is a continuation-in-part of non-
provisional application Ser. No. 09/788,201 filed Feb. 16,
2001, which claims the benefit under 35 U.S.C. 119(e) of
U.S. Provisional Application Serial No. 60/183,396 filed

TECHNICAL FIELD

[0002] The present invention is directed to the field of
synthesizing epoxides of steroids.

BACKGROUND OF THE INVENTION

[0003] Steroid epoxides are an important class of oxy-
sterols (oxygenated derivatives of cholesterol) involved in
the regulation of cell proliferation and cholesterol homeostasis.
They are versatile intermediates for steroid synthesis and
useful probes for biochemical studies of enzymes. Steroid
epoxides are also useful intermediates for the preparation of
other oxy steroids. For example, alpha- and-beta-epoxides of
cholesterol are auto-oxidation products of cholesterol in vivo,
and both are cytotoxic and mutagenic. The isomeric alpha-
and-beta-epoxides are hydrolysed by cholesterol 5,6-epoxide
hydrolyase to cholestane-3beta,5alpha,6beta-triol which has potent
hypcholesterolemic activity. On the other hand, both
epoxides inhibit the cholesterol 7alpha-hydroxylase which cataly-
izes the rate-determining step of bile acid synthesis. As 5alpha,
6alpha-epoxides are readily available via epoxidation of
Delta5-unsaturated steroids with peracids, there have been
extensive studies on the biological actions of those epoxides
and their derivatives. In contrast, much less is known about
the 5beta,6beta-epoxides and their derivatives because they are
difficult to obtain in high selectivity. More importantly, the
5beta,6beta-epoxy functionality is found in a number of naturally
occurring steroids of antitumor activities, e.g., jaborosalacto-
ne A, withaferin A, and withanolide D.

[0004] Common organic oxidants such as 3-chloroperoxy-
benzoic acid (mCPBA) generally give alpha-epoxides as the
major products for epoxidation of 3beta-substituted Delta5-steroids
and show poor selectivities for epoxidation of 3alpha-
substituted Delta5-steroids except epi-cholesterol. This is because
peracid epoxidation follows a concerted pathway via spiro
transition states (beta- and beta-IT (TS=transition state); see
FIG. 1). The beta-IT suffers from steric interactions between
the peracid and the C(10) angular methyl group for epoxidation
of 3beta-substituted Delta5-steroids, while both the beta-IT
and the alpha-IT encounter similar steric hindrance for epoxi-
dation of 3alpha-substituted Delta5-steroids. Dioxiranes are new-
generation reagents for oxidation under mild and neutral
conditions. Unfortunately, poor selectivities were reported
in epoxidation of 3beta-substituted Delta5-steroids by either iso-
lated or in situ generated dioxiranes. While dioxiranes also
epoxidize olefins through a spiro TS, their steric environ-
ment is different from that of peracids. To minimize steric
interactions, dioxiranes prefer to approach the C(5)–C(6)
double bond of Delta5-steroids from the less-substituted side,
i.e., away from the C(10)-angular methyl group and the
C-ring of steroids (FIG. 1). Therefore, it is the potential
steric interactions between the alpha-substituents of dioxiranes
and the 3alpha and 4beta substituents of steroids that determine
the facial selectivity of epoxidation.

[0005] Yang et al., in U.S. Pat. No. 5,763,623 and in J.
epoxidation of unfunctionalized olefins using various
ketones. These references do not teach or suggest the
epoxidation of Delta5-unsaturated steroids.

pages 2670-2673, disclose the epoxidation of a Delta5-
unsaturated steroid that is not a 3alpha-substituted Delta5-
unsaturated steroid, and in which the ketone catalyst is acetone.

32, pages 533-536, disclose the epoxidation reactions of four
Delta5-unsaturated steroids that are not 3alpha-substituted Delta5-
unsaturated steroids, and using a variety of ketones. In these
reactions either no epoxide was observed, or the Delta5-
epoxide ratio was about 1:1.

pages 2182-2184, disclose the epoxidation of a Delta5-
unsaturated steroid that is not a 3alpha-substituted Delta5-
unsaturated steroid, and using dimethylidioxirane. The Delta5-epoxide ratio
was about 3:1.

39, pages 1839-1842, disclose the epoxidation of a Delta5-
unsaturated steroid that is not a 3alpha-substituted Delta5-
unsaturated steroid, and using a variety of ketone catalysts.

Feb. 22, 2001, discloses an epoxidation method combining an olefin substrate, a ketone catalyst, a nitrile compound, and
hydrogen peroxide.

16, 1998, discloses the use of a chiral ketal and an oxidizing
agent with an olefin to generate an epoxide with high enan-
tiotericselectivity.

SUMMARY OF THE INVENTION

[0012] In accordance with the invention, a method is
provided for producing mostly 5beta,6beta-epoxides of Delta5-
unsaturated steroids using certain ketones as the catalyst along
with an oxidizing agent, or by using certain dioxiranes. In
another aspect of the invention, a method is provided for
producing mostly 5beta,6beta-epoxides of steroids from Delta5-
unsaturated steroids having a substituent at the 3alpha-position
by an epoxidation reaction using a ketone along with an
oxidizing agent under conditions effective to generate epoxides,
or using a dioxirane under conditions effective to generate
epoxides.

[0013] A whole range of Delta5-unsaturated steroids, bearing
different functional groups such as hydroxy, carboxyl, acetyl
or ketal group, as well as different side chains, are converted
to the corresponding synthetically and biologically interesting
5beta,6beta-epoxides with excellent beta-selectivities and high
yields.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] FIG. 1 is a diagrammatic representation of the
general epoxidation reaction between Delta5-unsaturated ste-
roids and mCPBA or dioxirane;
FIG. 2 is a listing of chemical structures corresponding to ketones 1-4 and steroids 5-20;

FIG. 3 is a diagrammatic representation of the epoxidation reaction of the present invention; and

FIGS. 4-70 are 1H NMR spectra of 5β,6β-epoxides of steroids and 3α,6α-epoxides of steroids including those epoxides of steroids synthesized as products by the method of the present invention and purified epoxides of steroids used as comparative control standards (referred to as "authentic samples").

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides highly β-selective epoxidation of Δ3-unsaturated steroids catalyzed by ketones or mediated by dioxiranes. More specifically, the present invention demonstrates that high β-selectivity can be achieved by increasing the steric size of either the α-substituents of dioxiranes or the 3α-substituents of Δ3-steroids. In some embodiments of the invention, the epoxidation reaction can provide said epoxides in at least about 5:1β:α-epoxide ratio.

In one aspect of the invention, a method of producing mostly 5β,6β-epoxides of steroids from Δ3-unsaturated steroids comprises an epoxidation reaction using a ketone and an oxidizing agent under conditions effective to generate epoxides, wherein the ketone is selected from compounds of generic formula I,

\[ R_1 R_2 R_3 R_4 R_5 R_6 R_7 R_8 R_9 R_{10} \]

[0020] where R₁ or R₂, in formula (I) is selected from alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOOR (where R=alkyl or aryl), OCOOCHR (where R=aryl), OCONRR₂, where R₁ or R₂=H, alkyl or aryl), OSi₃R₂R₃ (where R₁, R₂ or R₃=alkyl or aryl), and halogen;

[0021] R₃ or R₄ in formula (I) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOOR (where R=alkyl or aryl), OCOOCHR (where R=aryl), OCONRR₂, where R₁ or R₂=H, alkyl or aryl), OSi₃R₂R₃ (where R₁, R₂ or R₃=alkyl or aryl), and halogen;

[0022] R₅, R₆, R₇, or R₈ in formula (I) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONRR₂, where R₁ or R₂=H, alkyl or aryl);

[0023] R₉ or R₁₀ in formula (I) is selected from alkyl, halogenated alkyl, and aryl; and

[0024] A in formula (I) is selected from halogen, OTf, BF₃, OAc, NO₃, BPh₃, PF₅, and SbF₆.

[0025] In another aspect of the invention, a method of producing mostly 5β,6β-epoxides of steroids from Δ3-unsaturated steroids having a substituent at the 3α-position comprises an epoxidation reaction using a ketone and an oxidizing agent under conditions effective to generate epoxides. The substituent at the 3α-position can be selected from OR (where R=H, alkyl or aryl), O(CH₂)ₙOR (where n=1, 2 or 3, n=0, 1, 2 or R=H, alkyl or aryl), OSi₃R₂R₃ (where R₁, R₂ or R₃=alkyl or aryl), OSO₃R (where n=0, 1 or 2, R=H, alkyl or aryl), OCOOCHR (where n=1 or 2, R=H, alkyl or aryl), OCONRR₂ (where R₁ or R₂=H, alkyl or aryl), OPOR (where n=2 or 3, R=alkyl or aryl), NR₃R₂ (where R₁ or R₂=H, alkyl or aryl), NR₃CO₂R₂ (where n=1 or 2, R=H, alkyl or aryl), NR₃CONRR₂ (where R₃, R₂ or R₁=H, alkyl or aryl), NR₃SO₃R₂ (where n=1 or 2, R=H, alkyl or aryl), NR₃=alkyl or aryl), NPh₃ (Ph=phthaloyl group), NR₃R₂R₃ (where R₁, R₂ or R₃=H, alkyl or aryl), SiR₃R₂R₃ (where R₁, R₂ or R₃=H, alkyl or aryl), SO₂R (where n=0, 1 or 2, R=H, alkyl or aryl), SCO₂R (where n=1 or 2, R=H, alkyl or aryl), halogen, CN, NO₂, alkyl, COOR (where R=H, alkyl or aryl), and CONR₃R₂ (where R₁ or R₂=H, alkyl or aryl).

[0026] Further in accordance with this aspect of the invention, the Δ3-unsaturated steroid having a substituent at the 3α-position can be selected from the group consisting of Δ3-unsaturated steroids having a ketone group or a thio-ketone derivative of ketone group at the 3-position.

[0027] Further in accordance with this aspect of the invention, the ketone used in the epoxidation reaction can be selected from the group consisting of compounds of generic formula II, III, IV, and V wherein

\[ R_1 R_2 R_3 R_4 R_5 R_6 R_7 R_8 R_9 R_{10} \]

[0028] R₁, R₂, R₃, or R₄ in formula (II) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOOR (where R=alkyl or aryl), OCOOCHR (where R=aryl), OCONRR₂, where R₁ or R₂=H, alkyl or aryl), OSi₃R₂R₃ (where R₁, R₂ or R₃=alkyl or aryl), and halogen;

[0029] R₅, R₆, R₇, or R₈ in formula (II) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONRR₂, where R₁ or R₂=H, alkyl or aryl);

[0030] R₉ or R₁₀ in formula (II) is selected from halogen, OTf, BF₃, OAc, NO₃, BPh₃, PF₅, and SbF₆.
X in formula (III) is selected from (CR,R1)n (where n=1, 2, 3, 4, or 5; R1 or Rn=H, alkyl or aryl), O, S, SO, SO2, and NR (where R=H, alkyl or aryl);

R1, R2, R3, or R4 in formula (III) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOR (where R=H, alkyl or aryl), OOOCR (where R=alkyl or aryl), OCONR,R5 (where R1 or R5=H, alkyl or aryl), OSIR,R6,R7 (where R1, R2, or R4=alkyl or aryl), and halogen;

R15, R16, R17, or R18 in formula (III) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR,R2 (where R1 or R2=H, alkyl or aryl);

R15 or R20 in formula (IV) is selected from alkyl, halogenated alkyl, aryl, CR,R5,OCOR (where R1, R5, or R6=H, alkyl or aryl), CR,R5,OCOCR (where R1 or R6=H, alkyl or aryl; R2=alkyl or aryl), CR,R5,NCOR (where R1, R2, or R6=H, alkyl or aryl), CR,R5,NCOCR (where R1, R2, or R6=H, alkyl or aryl), CR,R5,NCOR (where R1, R2, or R6=H, alkyl or aryl), and CR,R5,NCOCR (where R1, R2, or R6=H, alkyl or aryl; R3=alkyl or aryl); and

Y in formula (V) is selected from H, alkyl, halogenated alkyl, aryl, NO2, CN, F, Cl, Br, I, COOR (where R=H or alkyl), OR (where R=H, alkyl or aryl), OSO2,R (where R=H, alkyl or aryl), OSOR (where R=H, alkyl or aryl), OSIR (where R=H, alkyl or aryl), S0,R (where R=H, alkyl or aryl), SO,R (where R=H, alkyl or aryl), SOON

R1, R2, R3 (where R1 or R3=H, alkyl or aryl), NR,SOOR (where R=H, alkyl or aryl; R2=alkyl or aryl), NR,SOR (where R=H, alkyl or aryl; R2=alkyl or aryl), CR,R5,OR (where R1, R2, or R6=H, alkyl or aryl), CR,(OR,R5) (where R1, R2=H or alkyl; R5=alkyl), CF3, CF2CF3, OTf, OTf5, OCOR (where R=H, alkyl or aryl), and OSIR,R6,R7 (where R1, R2, or R4=alkyl or aryl).

In yet another aspect of the invention, a method of producing mostly 5,6β-epoxides of steroids from Δ4-unsaturated steroids comprises an epoxidation reaction using a dioxirane under conditions effective to generate epoxides, wherein said dioxirane is selected from compounds of generic formula VI.

[0037] R1 or R4 in formula (VI) is selected from alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOR (where R=H, alkyl or aryl), OCOOR (where R=alkyl or aryl), OCONR,R3 (where R1 or R3=H, alkyl or aryl), OSOR,R2,R4 (where R1, R2, or R4=alkyl or aryl), and halogen;

[0038] R2 or R3 in formula (VI) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOOR (where R=alkyl or aryl), OCOOCR (where R=aryl), OCONR,R3 (where R1 or R3=H, alkyl or aryl), OSIR,R2,R4 (where R1, R2, or R4=alkyl or aryl), and halogen;

[0039] R5, R6, R7, or R8 in formula (VI) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR,R3 (where R1 or R3=H, alkyl or aryl);

[0040] R6 or R20 in formula (VI) is selected from alkyl, halogenated alkyl, and aryl; and

[0041] A in formula (VI) is selected from halogen, OTf, BF3, OAc, NO3, BPh4, PF6, and SbF6;

[0042] The dioxirane can be generated in situ from a ketone and an oxidizing agent selected from potassium peroxomonosulfate, sodium hypochlorite, sodium perborate, hydrogen peroxide, and peracids, wherein said ketone is selected from compounds of generic formula I,

A in formula (VI) is selected from halogen, OTf, BF3, OAc, NO3, BPh4, PF6, and SbF6;
[0043] \( R_1 \) or \( R_4 \) in formula (I) is selected from alkyl, halogenated alkyl, aryl, OR (where \( R=H \), alkyl or aryl), OCOR (where \( R=H \), alkyl or aryl), OCOOR (where \( R=alkyl \) or aryl), OCOOCH\( _2 \)R (where \( R=alkyl \) or aryl), OCONR\( _2 \)R\( _2 \) (where \( R_1 \) or \( R_\_2=H \), alkyl or aryl), OSiR\( _3 \)R\( _3 \) (where \( R_1 \), \( R_2 \) or \( R_\_3=alkyl \) or aryl), and halogen;

[0044] \( R_3 \) or \( R_6 \) in formula (I) is selected from \( H \), alkyl, halogenated alkyl, aryl, OR (where \( R=H \), alkyl or aryl), OCOR (where \( R=H \), alkyl or aryl), OCOOR (where \( R=alkyl \) or aryl), OCOOCH\( _2 \)R (where \( R=alkyl \) or aryl), OCONR\( _2 \)R\( _2 \) (where \( R_1 \) or \( R_\_2=H \), alkyl or aryl), OSiR\( _3 \)R\( _3 \) (where \( R_1 \), \( R_2 \) or \( R_\_3=alkyl \) or aryl), and halogen;

[0045] \( R_2, R_3, R_6, \) or \( R_8 \) in formula (I) is selected from \( H \), alkyl, halogenated alkyl, aryl, COOR (where \( R=H \), alkyl or aryl), and CON\( _\_2 \)R\( _2 \) (where \( R_1 \) or \( R_\_2=H \), alkyl or aryl);

[0046] \( R_8 \) or \( R_{10} \) in formula (I) is selected from alkyl, halogenated alkyl, and aryl;

[0047] A in formula (I) is selected from halogen, OTf, BF\( _3 \), OAc, NO\( _3 \), BPh\( _3 \), PF\( _3 \), and SbF\( _3 \);

[0048] In yet another aspect of the invention, a method of producing mostly 5\( \beta \),6\( \beta \)-epoxides of steroids from \( \Delta^2 \)-unsaturated steroids having a substituent at the 3\( \alpha \)-position comprises an epoxidation reaction using a dioxirane under conditions effective to generate epoxides. In accordance with this aspect of the invention, the substituent at the 3\( \alpha \)-position can be selected from OR (where \( R=H \), alkyl or aryl), \( O(CH_2)_n \)OR (where \( n=1, 2 \) or 3; \( R=H \), alkyl or aryl), \( O(CH_2)_n \)SO\( _3 \)R (where \( n=1, 2 \) or 3; \( R=H \), alkyl or aryl), OSiR\( _3 \)R\( _3 \) (where \( R_1 \), \( R_2 \) or \( R_\_3=alkyl \) or aryl), OCOOCH\( _2 \)R (where \( \alpha=H \), alkyl or aryl), OCOOR (where \( \alpha=H \), alkyl or aryl), OCONR\( _2 \)R\( _2 \) (where \( R_1 \) or \( R_\_2=H \), alkyl or aryl), OPO\( _3 \)R (where \( \alpha=H \), alkyl or aryl), NR\( _2 \)R\( _2 \) (where \( R_1 \) or \( R_\_2=H \), alkyl or aryl), NR\( _\_2 \)R\( _2 \) (where \( \beta=H \), alkyl or aryl), NCO\( _\_2 \)R\( _2 \) (where \( \gamma=H \), alkyl or aryl), NCH\( _\_2 \)R\( _2 \) (where \( \delta=H \), alkyl or aryl), NF\( _\_2 \)R\( _2 \) (where \( \epsilon=H \), alkyl or aryl), NC\( _\_2 \)R\( _2 \) (where \( \zeta=H \), alkyl or aryl), OSiR\( _3 \)R\( _3 \) (where \( R_1 \), \( R_2 \) or \( R_\_3=alkyl \) or aryl), SO\( _3 \)R (where \( \eta=H \), alkyl or aryl), SCON\( _2 \)R (where \( \eta=H \), alkyl or aryl), halogen, CN, NO\( _3 \), alkyl, aryl, COOR (where \( R=H \), alkyl or aryl), and CON\( _\_2 \)R\( _2 \) (where \( R_1 \) or \( R_\_2=H \), alkyl or aryl).

[0049] Further in accordance with this aspect of the invention, the \( \Delta^2 \)-unsaturated steroid having a substituent at the 3\( \alpha \)-position can be selected from the group consisting of \( \Delta^2 \)-unsaturated steroids having a ketal derivative of a ketone group or a thiketal derivative of a ketone group at the 3-position.

[0050] Further in accordance with this aspect of the invention, the dioxirane can be selected from the group consisting of compounds of generic formula VII, VIII, IX and X.

[0051] \( R_1, R_2, R_3, \) or \( R_4 \) in formula (VII) is selected from \( H \), alkyl, halogenated alkyl, aryl, OR (where \( R=H \), alkyl or aryl), OCOR (where \( R=H \), alkyl or aryl), OCOOR (where \( R=alkyl \) or aryl), OCOOCH\( _2 \)R (where \( R=alkyl \) or aryl), OCONR\( _2 \)R\( _2 \) (where \( R_1 \) or \( R_\_2=H \), alkyl or aryl), OSiR\( _3 \)R\( _3 \) (where \( R_1 \), \( R_2 \) or \( R_\_3=alkyl \) or aryl), and halogen;

[0052] \( R_2, R_3, R_6, R_8, R_9 \) or \( R_{10} \) in formula (VII) is selected from \( H \), alkyl, halogenated alkyl, aryl, COOR (where \( R=H \), alkyl or aryl), and CON\( _\_2 \)R\( _2 \) (where \( R_1 \) or \( R_\_2=H \), alkyl or aryl);

[0053] A in formula (VIII) is selected from halogen, OTf, BF\( _3 \), OAc, NO\( _3 \), BPh\( _3 \), PF\( _3 \), and SbF\( _3 \);

[0054] X in formula (VIII) is selected from \( (CR_3)_n \) (where \( n=1, 2, 3, 4, 5; \) \( R_1 \), \( R_2 \) or \( R_\_3=H \), alkyl or aryl), O, S, SO\( _2 \), and NR (where \( R=H \), alkyl or aryl);

[0055] \( R_1, R_2, R_3, \) or \( R_4 \) in formula (VIII) is selected from \( H \), alkyl, halogenated alkyl, aryl, OR (where \( R=H \), alkyl or aryl), OCOR (where \( R=H \), alkyl or aryl), OCOOR (where \( R=alkyl \) or aryl), OCOOCH\( _2 \)R (where \( R=alkyl \) or aryl), OCONR\( _2 \)R\( _2 \) (where \( R_1 \) or \( R_\_2=H \), alkyl or aryl), OSiR\( _3 \)R\( _3 \) (where \( R_1 \), \( R_2 \) or \( R_\_3=alkyl \) or aryl), and halogen;

[0056] \( R_1, R_2, R_3, \) or \( R_4 \) in formula (VIII) is selected from \( H \), alkyl, halogenated alkyl, aryl, COOR (where \( R=H \), alkyl or aryl), and CON\( _\_2 \)R\( _2 \) (where \( R_1 \) or \( R_\_2=H \), alkyl or aryl);

[0057] \( R_19 \) or \( R_20 \) in formula (IX) is selected from alkyl, halogenated alkyl, aryl, CR\( _3 \)R\( _3 \)OCOR\( _3 \) (where \( R_1 \), \( R_2 \) or \( R_\_3=H \), alkyl or aryl), CR\( _3 \)R\( _3 \)OCOOR\( _3 \) (where \( R_1 \) or \( R_\_3=H \),}
alkyl or aryl; \( R_1, R_2, \) or \( R_3 = \text{H} \), alkyl or aryl, \( R_4 = \text{alkyl or aryl} \), CR\(_n\)R\(_1\)NR\(_2\)COOR\(_3\) (where \( R_1, R_2, \) or \( R_3 = \text{H} \), alkyl or aryl, \( R_4 = \text{alkyl or aryl} \), CR\(_n\)R\(_1\)NR\(_2\)COR\(_3\) (where \( R_1, R_2, \) or \( R_3 = \text{H} \), alkyl or aryl), CR\(_n\)R\(_1\)NR\(_2\)SO\(_2\)R\(_3\) (where \( R_1, R_2, \) or \( R_3 = \text{H} \), alkyl or aryl, \( R_4 = \text{alkyl or aryl} \); and

\[ \text{[0062]} \quad \text{A in formula (II) is selected from halogen, OTf, BF}_4^-, \text{OAc, NO}_2^-, \text{BPh}_4^-, \text{PF}_6^-, \text{and SbF}_6^-. \]

\[ \text{[0063]} \quad \text{X in formula (III) is selected from (CR\(_n\)R\(_2\))}_n \text{ (where n=1, 2, 3, 4, or 5; R\(_1, \) or R\(_2 = \text{H} \), alkyl or aryl), O, S, SO, SO\(_2\), and NR (where R = H, alkyl or aryl);} \]

\[ \text{[0064]} \quad \text{R}_{15}, \text{R}_{16}, \text{R}_{17}, \text{or R}_{18} \text{ in formula (III) is selected from H, alkyl, halogenated alkyl,} \]

\[ \text{[0065]} \quad \text{R}_{15}, \text{R}_{16}, \text{R}_{17}, \text{or R}_{18} \text{ in formula (III) is selected from H, alkyl, halogenated alkyl,} \]

\[ \text{[0066]} \quad \text{R}_{15} \text{ or R}_{16} \text{ in formula (IV) is selected from alkyl,} \]

\[ \text{[0067]} \quad \text{Y in formula (V) is selected from H, alkyl, halogenated alkyl,} \]

\[ \text{[0058]} \quad \text{Y in formula (X) is selected from H, alkyl, halogenated alkyl,} \]

\[ \text{[0059]} \quad \text{The dioxirane can be generated in situ from a} \]

\[ \text{[0060]} \quad \text{R}_1, \text{R}_2, \text{R}_3, \text{or R}_4 \text{ in formula (II) is selected from H,} \]

\[ \text{[0061]} \quad \text{R}_1, \text{R}_2, \text{R}_3, \text{or R}_4 \text{ in formula (II) is selected from H,} \]

\[ \text{[0062]} \quad \text{A in formula (II) is selected from halogen, OTf,} \]

\[ \text{[0063]} \quad \text{X in formula (III) is selected from (CR\(_n\)R\(_2\))}_n \text{ (where n=1, 2, 3, 4, or 5; R\(_1, \) or R\(_2 = \text{H} \), alkyl or aryl), O, S, SO, SO\(_2\), and NR (where R = H, alkyl or aryl);} \]

\[ \text{[0064]} \quad \text{R}_{15}, \text{R}_{16}, \text{R}_{17}, \text{or R}_{18} \text{ in formula (III) is selected from H, alkyl, halogenated alkyl,} \]

\[ \text{[0065]} \quad \text{R}_{15}, \text{R}_{16}, \text{R}_{17}, \text{or R}_{18} \text{ in formula (III) is selected from H, alkyl, halogenated alkyl,} \]

\[ \text{[0066]} \quad \text{R}_1 \text{ or R}_2 \text{ in formula (IV) is selected from alkyl,} \]

\[ \text{[0067]} \quad \text{Y in formula (V) is selected from H, alkyl, halogenated alkyl,} \]

\[ \text{[0060]} \quad \text{R}_1, \text{R}_2, \text{R}_3, \text{or R}_4 \text{ in formula (II) is selected from H,} \]

\[ \text{[0061]} \quad \text{R}_1, \text{R}_2, \text{R}_3, \text{or R}_4 \text{ in formula (II) is selected from H,} \]

\[ \text{[0062]} \quad \text{A in formula (II) is selected from halogen, OTf,} \]

\[ \text{[0063]} \quad \text{X in formula (III) is selected from (CR\(_n\)R\(_2\))}_n \text{ (where n=1, 2, 3, 4, or 5; R\(_1, \) or R\(_2 = \text{H} \), alkyl or aryl), O, S, SO, SO\(_2\), and NR (where R = H, alkyl or aryl);} \]

\[ \text{[0064]} \quad \text{R}_{15}, \text{R}_{16}, \text{R}_{17}, \text{or R}_{18} \text{ in formula (III) is selected from H, alkyl, halogenated alkyl,} \]

\[ \text{[0065]} \quad \text{R}_{15}, \text{R}_{16}, \text{R}_{17}, \text{or R}_{18} \text{ in formula (III) is selected from H, alkyl, halogenated alkyl,} \]

\[ \text{[0066]} \quad \text{R}_1 \text{ or R}_2 \text{ in formula (IV) is selected from alkyl,} \]

\[ \text{[0067]} \quad \text{Y in formula (V) is selected from H, alkyl, halogenated alkyl,} \]
alkyl or aryl), SO₂R (where R=alkyl or aryl), SO₂N(R=alkyl or aryl), R₂H (where R₁=alkyl or aryl; R₆=alkyl or aryl), NR₂SO₂R₂ (where R₁=alkyl or aryl; R₆=alkyl or aryl), CR₂=SO₃R (where R₁=alkyl or aryl; R₆=alkyl or aryl), CR₂=CF₃ or CF₃CF₃ (where R₁=alkyl or aryl; R₆=alkyl or aryl), OSiR₂R₂R₂ (where R₁=alkyl or aryl; R₆=alkyl or aryl), and OSiR₂R₂R₂ (where R₁=alkyl or aryl; R₆=alkyl or aryl).

[0068] Epoxidation reactions in accordance with the invention and using dioxiranes can be carried out in solution or in a solvent from acetonitrile, dimethyloxirane, acetone, dioctane, dimethyloxirane, tetrahydrofuran, dichloromethane, chloroform, benzene, toluene, dimethylether, water and mixtures thereof.

[0069] In accordance with one embodiment of the invention herein, a method of producing mostly 5β,6β-epoxides of steroids comprises epoxidation reactions of Δ₅ unsaturated steroids of generic formula XI catalyzed by ketones of generic formula XII, wherein

![Diagram XI](Image)

[0070] X₁ in formula (XI) is selected from H, OR (where R=alkyl or alkyl), OCH₂CH₂O, OCOR (where R=alkyl or aryl), OSiR₂R₂ (where R₁=alkyl or aryl), halogen, CN, alkyl, aryl, and COOR (where R=H, alkyl or aryl);

[0071] R₁ in formula (XI) is selected from H, OR (where R=alkyl or alkyl), OCH₂CH₂O, OCOR (where R=alkyl or aryl), OSiR₂R₂ (where R₁=alkyl or aryl), halogen, CN, alkyl, aryl, and COOR (where R=H, alkyl or aryl);

[0072] R₂ and R₃ in formula (XI) are each selected from the group consisting of H, OR (where R=alkyl or alkyl), OCH₂CH₂O, OCOR (where R=alkyl or aryl), OSiR₂R₂ (where R₁=alkyl or aryl), halogen, CN, alkyl, aryl, and COOR (where R=H, alkyl or aryl);

[0073] R₄ in formula (XI) is selected from H, C₃-H₄, alkyl, halogen, OR (where R=H or alkyl), OCH₂CH₂O, OCOR (where R=alkyl or alkyl), OSiR₂R₂ (where R₁=alkyl or aryl), or OSiR₂R₂ (where R₁=alkyl or aryl);

[0074] R₅ in formula (XI) is selected from H, C₃-H₄, alkyl, halogen, OR (where R=H or alkyl), OCH₂CH₂O, OCOR (where R=alkyl or alkyl), or OSiR₂R₂ (where R₁=alkyl or aryl), or OSiR₂R₂ (where R₁=alkyl or aryl);

[0075] R₆ in formula (XI) is selected from H, halogen, OR (where R=H or alkyl), and OCOR (where R=alkyl or aryl);

[0076] R₁ in formula (XI) is selected from H, halogen, OR (where R=H or alkyl), and OCOR (where R=alkyl or aryl);

[0077] R₄ and R₅ in formula (XI) are each selected from alkyl and aryl;

[0078] R₄ and R₅ in formula (XI) are each selected from H, alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR₂R₂ (where R₁=alkyl or aryl, OR (where R=H, alkyl or aryl));

[0079] R₄ and R₅ in formula (XI) are each selected from C₃-H₄, alkyl, halogenated alkyl, and halogen; and

[0080] A in formula (XI) is selected from OTH, BF₄, OAc, NO₂, BPH₃, PF₃, and SBF₇.

[0081] In another embodiment of the instant invention, a method of producing mostly 5β,6β-epoxides of steroids comprises epoxidation reactions of Δ₅ unsaturated steroids of generic formula XIII catalyzed by ketones of generic formula XIV, XV, XVI, and XVII, wherein

![Diagram XIII](Image)

[0082] X₂ in formula (XIII) is selected from the group consisting of H, OR (where R=H or alkyl), OCH₂CH₂O, OCOR (where R=alkyl or aryl), OSiR₂R₂ (where R₁, R₂=alkyl or aryl), halogen, CN, alkyl, aryl, and COOR (where R=H, alkyl or aryl), and,

[0083] X₂ in formula (XIII) is selected from the group consisting of OR (where R=H or alkyl), OCH₂CH₂O, OCOR (where R=alkyl or aryl), OSiR₂R₂ (where R₁, R₂=alkyl or aryl), halogen, CN, alkyl, aryl, and COOR (where R=H, alkyl or aryl), and,

[0084] X₂ and X₃ in formula (XIII) are selected from the group consisting of O, OCH₂CH₂O, and OCH₂CH₂CH₂O;

[0085] R₁ in formula (XIII) is selected from H, OR (where R=H or alkyl), OCH₂CH₂O, OCOR (where R=alkyl or aryl), OSiR₂R₂ (where R₁=alkyl or aryl), halogen, CN, alkyl, aryl, and COOR (where R=H, alkyl or aryl), OR (where R=H or alkyl), OCH₂CH₂O, OCOR (where R=alkyl or aryl), OSiR₂R₂ (where R₁=alkyl or aryl), halogen, CN, alkyl, aryl, and COOR (where R=H, alkyl or aryl), and,

[0086] R₁ and R₉ in formula (XIII) are each selected from the group consisting of H, alkyl, aryl, halogen, OR (where R=H or alkyl, OCH₂CH₂O, OCOR (where R=alkyl or aryl), OSiR₂R₂ (where R₁=alkyl or aryl), halogen, CN, alkyl, aryl, and COOR (where R=H, alkyl or aryl), and
COCH_2OR (where R=H or alkyl), COCH_2OCOR (where R=alkyl or aryl), COCH_2F, COOR (where R=H or alkyl), C(OCH_2CH_2O)R (where R=alkyl), C(OCH_2CH_2O)CH_2COR (where R=H or alkyl), C(OCH_2CH_2O)CH_2OCOR (where R=alkyl or aryl), and C(OCH_2CH_2O)CH_2F; or R_9 and R_10 in formula (XIII) are selected from the group consisting of O, OCH_2CH_2O, and OCH_2CH_2CH_2O;

R_{11} and R_{12} in formula (XIII) are each selected from the group consisting of H, C_1-C_4 alkyl halogen, OR (where R=H or alkyl), OCOR (where R=alkyl or aryl), and OSiR''_1R''_2R''_3 (where R''_1, R''_2, or R''_3=alkyl or aryl);

R_{13} and R_{14} in formula (XIII) are each selected from the group consisting of H, halogen, OR (where R=H or alkyl), and OCOR (where R=alkyl or aryl);

R_{15} or R_{16} in formula (XIV) is selected from alkyl and aryl;

R_{17} or R_{18} in formula (XIV) is selected from alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR_2 (where R_1 or R_2=H, alkyl or aryl);

R_{19} or R_{20} in formula (XIV) is selected from H, C_1-C_4 alkyl, halogenated alkyl, and halogen; and

A in formula (XIV) is selected from OTf, BF_4, OAc, NO_2, BPh_4, PF_6, and SbF_6;

Y in formula (XV) is selected from CH_2, O, S, SO_2, and NR (where R=H or alkyl);

R_{21} or R_{22} in formula (XV) is selected from H, alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR_2 (where R_1 or R_2=H, alkyl or aryl);

R_{23} or R_{24} in formula (XV) is selected from H, halogen, C_1-C_4 alkyl, halogenated alkyl, and OCOR (where R=alkyl or aryl);

Z in formula (XVII) is selected from H, C_1-C_4 alkyl, aryl, NO_2, CN, F, Cl, Br, I, COOR (where R=alkyl), CH_2OR (where R=H or alkyl), CH(OR)_2 (where R=alkyl), CF_3, CF_2CF_3, OTf, OTs, OCOR (where R=alkyl or aryl), and OSiR''_1R''_2R''_3 (where R''_1, R''_2, or R''_3=alkyl or aryl);

In each of the disclosed embodiments, C_1-C_4 alkyl can be selected from the group consisting of methyl, ethyl, normal-propyl, iso-propyl, normal-butyl, iso-butyl, sec-butyl, and tert-butyl; and said aryl can be selected from the group consisting of phenyl, substituted phenyl, naphthyl, and substituted naphthyl groups. The epoxidation reactions can be carried out in a homogeneous solvent system selected from the group consisting of dimethoxymethane-water, acetonitrile-water, acetone-water, dioxane-water, dimethoxymethane-water, and tetrahydrofuran-water, and mixtures thereof. Alternatively, the epoxidation reactions can be carried out in a biphasic solvent system selected from the group consisting of chloroform-water, benzene-water, toluene-water, dimethoxymethane-water, and diethylether-water and mixtures thereof.

Suitable oxidation agents for the epoxidation reactions of the instant invention include potassium peroxydisulfate, sodium hypochlorite, sodium perborate, hydrogen peroxide, and persic acid.

The epoxidation reactions of the instant invention catalyzed by a ketone can be carried out at a temperature within the range from about -10°C to about 40°C. Direct dioxirane epoxidation reactions of the instant invention can be carried out at a temperature within the range of from about -40°C to about 40°C. Some epoxidation reactions of the instant invention can be carried out at about room temperature.
[0014] The epoxidation reactions of the instant invention can be carried out at a pH within the range from about 7.0 to about 12.0. Some such epoxidation reactions can be carried out at a pH within the range from about 7.0 to about 7.5. The pH can be controlled by using a pH-stat machine such as is known in the art, or a buffer. Suitable buffers include solutions of sodium bicarbonate, sodium carbonate, sodium borate, sodium hydrogenphospate, sodium dihydrogenphosphate, sodium hydroxide, potassium hydrogenphosphate, potassium dihydrogenphosphate, potassium bicarbonate, potassium carbonate and potassium hydroxide.

[0022] We first examined four efficient ketone catalysts 1-4 for the in situ epoxidation of cholesterol 5 (FIG. 2). A modified homogeneous solvent system (a mixture of DMM/CH₃CN/H₂O in a 3:1:2 ratio) was used to increase the solubility of steroid substrates (FIG. 3). The results are summarized in Table 1. The ratio of β/α-epoxides was determined by integration of the (C­6) proton signals in the ¹H NMR spectra of the crude residues (63.00-3.15 ppm for β-epoxides and 67.2.75-2.95 ppm for α-epoxides). While ketones 1-3 exhibited poor β-selectivities (β/α epoxide ratio ca. 1:1; entries 1-3), ketone 4 with the most bulky α-substituent gave the best β-selectivity (β/α epoxide ratio 15:1; entry 4). A variety of 3β-substituted Δ5-steroids 6-10 (FIG. 2) were then subjected to the in situ epoxidation conditions with 20-30 mol % of ketone 4. The results revealed that ketone 4 generally gave high β-selectivities (β/α epoxide ratio >8:5:1) and high yields (entries 4-10). It is interesting to note that Δ5-steroids with a free C3-OH group were directly converted to their 5β,6β-epoxides with high selectivity and yields (entries 4, 5, and 7-9). (Note: The free 3-OH group of Δ5-unsaturated steroids is not compatible with some metal-based oxidants in the oxidation reactions.) Meanwhile, a wide range of functional groups such as hydroxyl, methoxyl, methoxymethyl ether, and carbonyl group were well tolerated under the mild and neutral reaction conditions (room temperature, pH 7-7.5).

[0036] Epoxidation reactions of 3α-substituted Δ5-steroids 11-20 were also carried out with ketone catalysts 1-4 (FIG. 2) and the ketone catalyst acetone. For epicholesterol 11 with a 3α-OH group, the epoxidation reactions catalyzed by ketones 1 and 4 gave much higher selectivities than those by ketones 2 and 3 (Table 2; entries 1-4) and acetone (see Table 3). This is because ketones 1 and 4 have larger α-substituents. For substrates with 3α-substituents larger than the OH group (12-20), the in situ epoxidation catalyzed by ketones 1-4 and acetone produced almost single 5β,6β-isomers (Table 2, β/α ratio >9:1, entries 5-24; Table 3). Substrates with 3-ketal group are of particular interest since highly α-selective epoxidation with trifluoroperacetic acid has been reported for this class of Δ5-steroids. Epoxidation of substrates 13-20 with mCPBA gave ca. 1:1 ratio of β/α-epoxides. The epoxidation reactions catalyzed by ketone 2 were highly efficient as only 5 mol % of the catalyst was needed even on a preparative scale. For example, a multi-gram scale (10 mmol) epoxidation of substrate 18 catalyzed by ketone 2 (5 mol %) provided almost a single β-epoxide (β/α-epoxide ratio >9:1) in 88% yield. These results clearly demonstrate the power of ketone-catalyzed epoxidation method.

[0044] In summary, we have developed a general, efficient and environmentally friendly method for highly β-selective epoxidation of Δ5-unsaturated steroids. With this method in hand, a library of 5β,6β-epoxides and their derivatives can be readily constructed and then screened for potential ligands that bind to orphan nuclear receptors. This is crucial for elucidating the biological functions of those receptors as well as for drug discovery.

General Experimental

[0056] The ¹H and ¹³C NMR spectra (FIGS. 4-7) were recorded in deuterochloroform (CDCl₃) with tetramethylsilane (TMS) as internal standard at ambient temperature on a Bruker Avance DPX 300 or 500 Fourier Transform Spectrometer. Infrared absorption spectra were recorded as a solution in CH₂Cl₂ on a Bio-Rad FTS 165 Fourier Transform Spectrophotometer. Mass spectra were recorded with a Finnigan MAT 95 mass spectrometer for both low resolution and high resolution mass spectra.

[0066] Substrates 5, 6, 8, 9, ketone 1, tetrahydrothiopyran-4-ione (precursor of ketone 2), and Oxone® were purchased from Aldrich or Acros Chemical Co. and used without further purification. Substrates 7, 10, 11, 12, 13, 20, and ketones 3, 4 were prepared according to the literature procedures.

Typical Procedure for in situ Epoxidation Reactions

[0076] Epoxidation of Cholesterol 5 Catalyzed by Ketone 4 (Table 1, Entry 4). To a solution of cholesterol 5 (116 mg, 0.3 mmol) and ketone 4 (41 mg, 0.09 mmol) in dimethoxy methane (DMM, 9 mL) and acetone (CH₂CN, 3 mL) at room temperature was added an aqueous Na₂-EDTA solution (6 mL, 4x10⁻⁴ M). To this mixture was added in portions a mixture of Oxone® (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) over the reaction period. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous MgSO₄ and filtered through a pad of silica gel. The ratio of α/β-epoxides was determined by ¹H NMR analysis of the crude residue which was obtained after removal of the solvent under reduced pressure. Pure products were obtained after flash column chromatography on silica gel (95 mg, 82% yield).

[0086] Epoxidation of Substrate 13 Catalyzed by Ketone 2 (Table 2, Entry 8). To a solution of substrate 13 (112 mg, 0.3 mmol) and tetrahydrothiopyran-4-ione (1.7 mg, 0.015 mmol) in dimethoxy methane (DMM, 9 mL) and acetone (CH₂CN, 3 mL) at room temperature was added an aqueous Na₂-EDTA solution (6 mL, 4x10⁻⁴ M). To this mixture was added in portions a mixture of Oxone® (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) over a period of 1.5 h. The reaction was complete in 2 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were...
were dried over anhydrous MgSO₄ and filtered through a pad of silica gel. The ratio of α/β-epoxides was determined by ¹H NMR analysis of the crude residue which was obtained after removal of the solvent under reduced pressure. Pure epoxide was obtained after flash column chromatography on silica gel (110 mg, 94% yield).

Procedure for Preparative Scale Epoxidation Reactions

[0109] Epoxidation of Substrate 9 Catalyzed by Ketone 4 (Table 1, Entry 9). To a solution of substrate 9 (3.17 g, 10 mmol) and ketone 4 (1.57 g, 3 mmol) in dimethoxy methane (DMM, 300 mL) and acetonitrile (CH₃CN, 100 mL) at room temperature was added an aqueous Na₂EDTA solution (200 mL, 4 x 10⁻⁴ M). To this mixture was added in portions a mixture of Ozone® (30.74 g, 50 mmol) and sodium bicarbonate (13.02 g, 155 mmol) over a period of 8 h. The reaction was complete in 10 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous MgSO₄ and filtered through a pad of silica gel. The ratio of α/β-epoxides was determined by ¹H NMR analysis of the crude residue which was obtained after removal of the solvent under reduced pressure. Pure products were obtained after flash column chromatography on silica gel (2.86 g, 86% yield).

[0110] Epoxidation of Substrate 18 Catalyzed by Ketone 2 (Table 2, Entry 19). To a solution of substrate 18 (4.03 g, 10 mmol) and tetrahydrothiopyran-4-one (58 mg, 0.5 mmol) in dimethoxy methane (DMM, 300 mL) and acetonitrile (CH₃CN, 100 mL) at room temperature was added an aqueous Na₂EDTA solution (200 mL, 4 x 10⁻⁴ M). To this mixture was added in portions a mixture of Ozone® (30.74 g, 50 mmol) and sodium bicarbonate (13.02 g, 155 mmol) over a period of 4 h. The reaction was complete in 5 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous MgSO₄ and filtered through a pad of silica gel. The ratio of α/β-epoxides was determined by ¹H NMR analysis of the crude residue which was obtained after removal of the solvent under reduced pressure. Pure epoxide was obtained after flash column chromatography on silica gel (3.68 g, 88% yield).

Characterization Data for Epoxides

[0112]

5a and 5b (as a mixture of 1:15.1 ratio; Table 1, Entry 4):

[0114] ¹H NMR (300 MHz, CDCl₃) δ 3.94-3.86 (m, 1/16.1×1H, 3α-H), 3.74-3.64 (m, 15.1/16.1×1H, 3α-H), 3.06 (d, J=2.2 Hz, 15.1/16.1×1H, 6α-H), 2.92 (d, J=4.3 Hz, 1/16.1×1H, 6β-H), 1.00 (s, 1/16.1×3H, 19-CH₃), 0.99 (s, 15.1/16.1×3H, 19-CH₃), 0.92 (d, J=6.6 Hz, 15.1/16.1×3H, 21-CH₃), 0.86 (d, J=6.6 Hz, 15.1/16.1×6H, 26-CH₃ and 27CH₃), 0.64 (s, 15.1/16.1×3H, 18-CH₃), 0.61 (s, 1/16.1×3H, 18-CH₃); ¹³C NMR of 5b (75.5 MHz, CDCl₃) δ 69.32, 63.76, 63.04, 56.21, 56.20, 51.32, 42.27, 42.18, 39.82, 39.48, 37.22, 36.12, 35.71, 34.84, 32.59, 30.97, 29.76, 28.14, 27.99, 24.18, 23.80, 22.81, 22.55, 21.98, 18.66, 17.05, 11.75.

General Procedure for Epoxidation of Δ⁴- Unsaturated Steroids with mCPBA

[0111] Sodium bicarbonate (0.4 mmol) and mCPBA (0.2 mmol) were added to a solution of substrate (0.1 mmol) in CH₂Cl₂ (3 mL). The resulting mixture was stirred at room temperature for 2 h and quenched with a solution of saturated aqueous Na₂S₂O₅. The reaction mixture was diluted with ethyl acetate and washed with a solution of saturated aqueous NaHCO₃ and brine. The organic layer was dried over anhydrous MgSO₄ and filtered through a pad of silica gel. The product analysis was performed as above.

[0115] 6a and 6b (as a mixture of 1:10.4 ratio; Table 1, Entry 5):

[0116] ¹H NMR (300 MHz, CDCl₃) δ 3.95-3.85 (m, 1/11.4×1H, 3α-H), 3.76-3.65 (m, 10.4/11.4×1H, 3α-H), 3.13
(d, J=2.5 Hz, 10.4/11.4×1H, 6α-H), 2.95 (d, J=4.3 Hz, 1/11.4×1H, 6β-H), 1.09 (s, 1/11.4×3H, 19-CH₃), 1.03 (s, 10.4/11.4×3H, 19-CH₃), 0.85 (s, 10.4/11.4×3H, 18-CH₃) 0.82 (s, 1/11.4×3H, 18-CH₃). 13C NMR of 6b (75.5 MHz, CDCl₃) δ 220.97, 69.21, 63.32, 63.05, 51.47, 51.18, 47.49, 42.05, 37.24, 35.74, 35.10, 31.51, 31.46, 30.93, 29.47, 21.73, 21.28, 17.08, 13.47.

[0119] 8a and 8b (as a mixture of 1:8:8 ratio; Table 1, Entry 7):

[0120] 1H NMR (300 MHz, CDCl₃) δ 8.95-3.84 (m, 1/9.8×1H, 3α-H), 3.74-3.64 (m, 8.8/9.8×1H, 3-CH₃), 3.60 (t, J=8.5 Hz, 1H, 17α-H), 3.07 (d, J=2.4 Hz, 8.8/9.8×1H, 6α-H), 2.91 (d, J=4.4 Hz, 1/9.8×3H, 6β-H), 1.07 (s, 1/9.8×3H, 19-CH₃), 1.01 (s, 8.8/9.8×3H, 19-CH₃), 0.72 (s, 8.8/9.8×3H, 18-CH₃), 0.69 (s, 1/9.8×3H, 18-CH₃). 13C NMR of 8b (75.5 MHz, CDCl₃) δ 881.81, 69.31, 63.51, 63.01, 51.48, 50.74, 42.67, 42.15, 37.25, 36.62, 34.99, 32.19, 30.97, 30.42, 29.81, 23.31, 21.60, 17.12, 10.86.

[0117] 7a and 7b (as a mixture of 1:9; Table 1, Entry 6):

[0118] 1H NMR (500 MHz, CDCl₃) δ=3.45-3.38 (m, 1/10×1H, 3α-H), 3.34 (s, 3H, OCH₃), 3.28-3.22 (m, 9/10×1H, 3α-H), 3.11 (d, J=2.4 Hz, 9/10×1H, 6α-H), 2.95 (d, J=4.4 Hz, 1/10×1H, 6β-H), 1.18 (s, 9/10×3H, 19-CH₃), 1.17 (s, 1/10×3H, 19-CH₃), 1.02 (s, 9/10×6H, 20-CH₃, and 21-CH₃), 0.87 (s, 9/10×3H, 18-CH₃), 0.85 (s, 1/10×3H, 18-CH₃). 13C NMR of 9b (75.5 MHz, CDCl₃) δ=225.00, 77.70, 63.15, 63.04, 55.71, 51.37, 48.52, 48.01, 45.15, 38.63, 37.82, 36.55, 35.54, 32.30, 31.66, 28.93, 27.27, 27.02, 25.95, 21.08, 17.13, 14.08; IR (CHCl₃) 1730 cm⁻¹; LRMS (EI, 20 eV) m/z 346 (100), 314 (15), 123 (31), 108 (22); HRMS (EI, 20 eV) calcd for C₃₀H₄₀N₂O₅ (M⁺): 346.2508, found: 346.2508; Anal. Calcd for C₃₀H₄₀N₂O₅: C, 76.26; H, 9.89; Found: C, 76.14; H, 9.90.

[0121] 9a and 9b (as a mixture of 1:11:6; Table 1, Entry 8):

[0122] 1H NMR (300 MHz, CDCl₃) δ 8.94-3.87 (m, 1/12.6×1H, 3α-H), 3.75-3.65 (m, 11.6/12.6×1H, 3α-H), 3.08 (d, J=2.3 Hz, 11.6/12.6×1H, 6α-H), 2.92 (d, J=4.4 Hz, 1/12.6×1H, 6α-H), 2.11 (s, 11.6/12.6×3H, 21-CH₃), 1.06 (s, 1/12.6×3H, 19-CH₃), 1.00 (s, 1/12.6×3H, 19-CH₃), 0.59 (s, 11.6/12.6×3H, 18-CH₃), 0.56 (s, 1/12.6×3H, 18-CH₃). 13C NMR of 9b (75.5 MHz, CDCl₃) δ 820.48, 69.29, 63.67, 63.50, 62.89, 56.33, 51.19, 43.89, 42.12, 38.84, 4.92, 32.51, 31.46, 30.97, 29.76, 24.36, 22.77, 21.96, 17.07, 13.11.
1H NMR (300 MHz, CDCl₃) δ 4.10-4.07 (m, 1H, 3β-H), 2.87 (d, J=4.5 Hz, 1H, 6β-H), 1.04 (s, 3H, 19-CH₃), 0.89 (d, J=6.6 Hz, 6H, 26-CH₃ and 27-CH₃), 0.61 (s, 3H, 18-CH₃). 13C NMR (75.5 MHz, CDCl₃) δ 79.98, 65.43, 57.79, 56.86, 55.84, 42.66, 42.32, 39.49, 39.36, 36.41, 36.13, 35.76, 35.52, 29.62, 28.92, 28.63, 28.59, 28.07, 28.00, 24.02, 23.84, 22.82, 22.56, 20.28, 18.64, 15.34, 11.86.

1H NMR (300 MHz, CDCl₃) δ 4.10-4.07 (m, 1H, 3β-H), 2.87 (d, J=4.5 Hz, 1H, 6β-H), 1.04 (s, 3H, 19-CH₃), 0.89 (d, J=6.6 Hz, 6H, 26-CH₃ and 27-CH₃), 0.61 (s, 3H, 18-CH₃). 13C NMR (75.5 MHz, CDCl₃) δ 79.98, 65.43, 57.79, 56.86, 55.84, 42.66, 42.32, 39.49, 39.36, 36.41, 36.13, 35.76, 35.52, 29.62, 28.92, 28.63, 28.59, 28.07, 28.00, 24.02, 23.84, 22.82, 22.56, 20.28, 18.64, 15.34, 11.86.
[0133] 14b:

[0134] $^1$H NMR (300 MHz, CDCl$_3$) δ 83.97-3.85 (m, 4H, OCH$_2$CH$_2$O), 3.05 (d, J=1.9 Hz, 1H, 6α-H), 0.99 (s, 3H, 19-CH$_3$), 0.89 (d, J=0.7 Hz, 3H, 21-CH$_3$), 0.86 (d, J=6.6 Hz, 6H, 26-CH$_2$ and 27-CH$_2$). $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 109.45, 64.27, 64.09, 63.29, 56.24, 56.15, 49.85, 42.28, 41.46, 39.81, 39.47, 36.11, 35.71, 35.61, 35.01, 32.27, 30.82, 29.67, 28.15, 27.98, 24.16, 23.79, 22.81, 22.54, 21.89, 18.66, 17.06, 11.75.

[0135] 15b:

[0136] $^1$H NMR (300 MHz, CDCl$_3$) δ 83.97-3.87 (m, 4H, OCH$_2$CH$_2$O), 3.60 (t, J=8.5 Hz, 1H, 17α-H), 3.07 (d, J=2.2 Hz, 1H, 6α-H), 1.01 (s, 3H, 19-CH$_3$), 0.72 (s, 3H, 18-CH$_3$). $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 109.41, 81.78, 64.31, 64.14, 63.14, 63.05, 50.70, 50.07, 42.70, 41.45, 36.63, 36.06, 35.17, 31.87, 30.81, 30.45, 29.73, 23.31, 21.53, 17.14, 10.88.

[0137] 16b:

[0138] $^1$H NMR (300 MHz, CDCl$_3$) δ 84.56 (dd, J=9.0, 7.9 Hz, 1H, 17α-H), 3.95-3.89 (m, 4H, OCH$_2$CH$_2$O), 3.07 (d, J=2.2 Hz, 1H, 6α-H), 2.03 (s, 3H, CH$_3$COO), 1.00 (s, 3H, 19-CH$_3$), 0.77 (s, 3H, 18-CH$_3$). $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 109.44, 65.16, 64.29, 64.12, 63.26, 63.19, 63.00, 58.21, 56.12, 49.87, 41.75, 9.44, 35.62, 35.06, 32.18, 30.82, 29.22, 24.54, 23.70, 22.90, 21.67, 17.10, 12.76.

[0139] 17b:

[0140] $^1$H NMR (300 MHz, CDCl$_3$) δ 83.95-3.90 (m, 4H, OCH$_2$CH$_2$O), 3.07 (d, J=2.1 Hz, 1H, 6α-H), 2.11 (s, 3H, 21-CH$_3$), 1.00 (s, 3H, 19-CH$_3$), 0.60 (s, 3H, 18-CH$_3$). $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 109.37, 64.33, 64.16, 63.66, 63.15, 62.25, 56.40, 49.84, 43.92, 41.42, 38.85, 35.71, 35.10, 32.21, 31.47, 30.82, 29.70, 24.36, 22.78, 21.90, 17.09, 13.12.

[0141] 18b:

[0142] $^1$H NMR (300 MHz, CDCl$_3$) δ 84.04-3.81 (m, 8H, OCH$_2$CH$_2$O), 3.06 (d, J=1.8 Hz, 1H, 6α-H), 1.28 (s, 3H, 19-CH$_3$), 1.00 (s, 3H, 18-CH$_3$). $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 109.44, 65.16, 64.29, 64.12, 63.26, 63.19, 63.00, 58.21, 56.12, 49.87, 41.75, 9.44, 35.62, 35.06, 32.18, 30.82, 29.22, 24.54, 23.70, 22.90, 21.67, 17.10, 12.76.

[0143] 19b:

[0144] $^1$H NMR (300 MHz, CDCl$_3$) δ 84.03-3.81 (m, 9H, 11β-H and OCH$_2$CH$_2$O), 3.08 (d, J=2.6 Hz, 1H, 6α-H), 1.28
(s, 3H, 21-CH₃), 1.20 (s, 3H, 19-CH₃), 0.76 (s, 3H, 18-CH₃);
¹³C NMR (75.5 MHz, CDCl₃) δ111.47, 109.02, 68.68, 64.98, 64.17, 64.04, 63.35, 63.10, 62.90, 57.80, 57.01, 55.22, 50.60, 42.45, 41.81, 37.41, 35.87, 31.40, 30.57, 27.91, 24.40, 23.42, 22.97, 15.55, 13.86.

Determination of the Ratio of β/α-epoxides

The ratio of β/α-epoxides was determined by integration of the C(6) proton signals in the ¹H NMR spectra (300 or 500 MHz) of crude residues (83.00-3.15 ppm for β-epoxides and 2.75-2.95 ppm for α-epoxides). The authentic samples of 5α/5β-20a/20b were prepared by epoxidation of substrates 5-20 with mCPBA according to the literature procedure.

EXAMPLES

Example 1

5β,6β-Epoxycholestan-3β-ol (Catalyzed by Ketone 4)

To a solution of cholesterol (116 mg 0.3 mmol) and ketone 4 (41 mg, 0.09 mmol) in dimethoxymethane (9 mL) and acetonitrile (3 mL) at room temperature was added an aqueous Na₂EDTA solution (6 mL, 4x10⁻⁴ M). This mixture was added in portions to Ozone® (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) over a period of 0.5 h. The reaction was complete in 1 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous MgSO₄ and filtered through a pad of silica gel. ¹H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was 15:1. Pure products were obtained after flash column chromatography on silica gel (99 mg, 82% yield).

Example 2

5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene Ketal (Catalyzed by Ketone 1)

To a solution of 5-androstene-3,17-dione 3,17-diethylene ketal (112 mg 0.3 mmol) in dimethoxymethane (9 mL) and acetonitrile (3 mL) was added an aqueous Na₂EDTA solution (6 mL, 4x10⁻⁴ M), the resulting solution was cooled to 0°C, followed by addition of 1,1,1-trifluoroaceton (0.54 mL, 6 mmol). To this solution was added in portions a mixture of Ozone® (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) over a period of 0.5 h. The reaction was complete in 1 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous MgSO₄ and filtered through a pad of silica gel. ¹H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was >99:1. 5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene ketal was obtained after flash column chromatography on silica gel (101 mg, 86% yield).

Example 3

5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene Ketal (Catalyzed by Ketone 2)

To a solution of 5-androstene-3,17-dione 3,17-diethylene ketal (112 mg 0.3 mmol) and tetrahydrothiopyran-4-one (1.7 mg, 0.015 mmol) in dimethoxymethane (9 mL) and acetonitrile (3 mL) at room temperature was added an aqueous Na₂EDTA solution (6 mL, 4x10⁻⁴ M). To this mixture was added in portions a mixture of Ozone® (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) over a period of 0.5 h. The reaction was complete in 2 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous MgSO₄ and filtered through a pad of silica gel. ¹H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was 96:1. 5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene ketal was obtained after flash column chromatography on silica gel (110 mg, 94% yield).

Example 4

5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene Ketal (Catalyzed by Ketone 3)

To a solution of 5-androstene-3,17-dione 3,17-diethylene ketal (112 mg 0.3 mmol) and ketone 3 (9 mg, 0.03 mmol) in dimethoxymethane (9 mL) and acetonitrile (3 mL) at room temperature was added an aqueous Na₂EDTA solution (6 mL, 4x10⁻⁴ M). To this mixture was added in portions a mixture of Ozone® (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) over a period of 1 h. The reaction was complete in 1.5 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous MgSO₄ and filtered through a pad of silica gel. ¹H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was 49:1. 5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene ketal was obtained after flash column chromatography on silica gel (109 mg, 93% yield).

Example 5

5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene Ketal (Catalyzed by Acetone)

To a solution of 5-androstene-3,17-dione 3,17-diethylene ketal (112 mg 0.3 mmol) and acetone (522 mg, 9
mmol) in dimethoxymethane (9 mL) and acetonitrile (3 mL) at room temperature was added an aqueous Na₂EDTA solution (6 mL, 4×10⁻⁴ M). To this mixture was added in portions a mixture of Oxone® (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) over a period of 4 h. The reaction was complete in 5 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous MgSO₄ and filtered through a pad of silica gel. ¹H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was >99:1. 5β,6β-Epoxyandrosten-3,17-dione 3,17-diethylene ketal was obtained after flash column chromatography on silica gel (110 mg, 94% yield).

Example 6
5β,6β-Epoxyandrosten-3,17-dione 3,17-diethylene Ketal (Acetone as Catalyst and Cosolvent)

[0153] To a solution of 5-androsten-3,17-dione 3,17-diethylene ketal (112 mg 0.3 mmol) in acetone (15 mL) at room temperature was added an aqueous Na₂EDTA solution (5 mL, 4×10⁻⁴ M). To this mixture was added in portions a mixture of Oxone® (922 mg, 1.5 mmol) and sodium bicarbonate (391 mg, 4.65 mmol) over a period of 1.5 h. The reaction was complete in 2 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous MgSO₄ and filtered through a pad of silica gel. ¹H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was >99:1. 5β,6β-Epoxyandrosten-3,17-dione 3,17-diethylene ketal was obtained after flash column chromatography on silica gel (105 mg, 90% yield).

Example 7
5β,6β-Epoxy-3β-hydroxyandrost-17-ene
(Catalyzed by Ketone 4)

[0154] To a solution of pregnenolonone (3.17 g 10 mmol) and ketone 4 (1.37 g, 3 mmol) in dimethoxymethane (300 mL) and acetonitrile (100 mL) at room temperature was added an aqueous Na₂EDTA solution (200 mL, 4×10⁻⁴ M). To this mixture was added in portions a mixture of Oxone® (30.74 g, 50 mmol) and sodium bicarbonate (13.02 g, 155 mmol) over a period of 8 h. The reaction was complete in 10 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous MgSO₄ and filtered through a pad of silica gel. ¹H NMR analysis of the product showed that the ratio of β/α-epoxides was 16.0:1. Pure products were obtained after flash column chromatography on silica gel (2.86 g, 86% yield).

Example 8
5β,6β-Epoxy-11α-hydroxypregnene-3,20-dione
3-diethylene Ketal (Catalyzed by Ketone 2)

[0155] To a solution of 5-pregene-3,20-dione 3,20-diethylen ketal (4.03 g 10 mmol) and tetrahydrothiopyran-4-one (58 mg, 0.5 mmol) in dimethoxymethane (300 mL) and acetonitrile (100 mL) at room temperature was added an aqueous Na₂EDTA solution (200 mL, 4×10⁻⁴ M). To this mixture was added in portions a mixture of Oxone® (30.74 mg, 50 mmol) and sodium bicarbonate (13.02 g, 155 mmol) over a period of 4 h. The reaction was complete in 5 h as shown by TLC. The reaction mixture was poured into water, and extracted with ethyl acetate three times. The combined organic layers were dried over anhydrous MgSO₄ and filtered through a pad of silica gel. ¹H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was >99:1. 5β,6β-Epoxyprogrenene-3,20-dione 3,20-diethylene ketal was obtained after flash column chromatography on silica gel (3.68 g, 88% yield).

Example 9
5β,6β-Epoxy-3β-hydroxyandrost-17-ene
(Catalyzed by Ketone 4)

[0156] Following the procedure of Example 1 above, dehydroisoandrosterone was epoxidized to 5β,6β-epoxy-3β-hydroxyandrost-17-ene.

Example 10
5β,6β-Epoxy-16,16-dimethyl-3β-methoxyandrost-17-ene
(Catalyzed by Ketone 4)

[0157] Following the procedure of Example 1 above, 16,16-dimethyl-3β-methoxy-5-androsten-17-ene was epoxidized to 5β,6β-epoxy-16,16-dimethyl-3β-methoxyandrost-17-ene.

Example 11
5β,6β-Epoxyandrostone-3β,17β-diol
(Catalyzed by Ketone 4)

[0158] Following the procedure of Example 1 above, 5-androstone-3β,17β-diol was epoxidized to 5β,6β-epoxyandrostone-3β,17β-diol.

Example 12
5β,6β-Epoxy-3β-methoxyethoxyandrost-20-one
(Catalyzed by Ketone 4)

[0159] Following the procedure of Example 1 above, 3β-methoxyethoxy-5-pregnen-20-one was epoxidized to 5β,6β-epoxy-3β-methoxyethoxyandrost-20-one.

Example 13
5β,6β-Epoxycholestan-3α-ol
(Catalyzed by Ketone 4)

[0160] Following the procedure of Example 1 above, epicholesterol was epoxidized to 5β,6β-epoxycholestan-3α-ol.

Example 14
5β,6β-Epoxy-3β-acetoxycholestan-3α-ol
(Catalyzed by Ketone 2)

[0161] Following the procedure of Example 3 above, 3α-acetoxycholestan-5-ene was epoxidized to 5β,6β-epoxy-3α-acetoxycholestan-3α-ol.
Example 15

5β,6β-Epoxy-3α-acetoxycholestan-5-one was epoxidized to 5β,6β-epoxy-3α-acetoxycholestan.

Example 16

5β,6β-Epoxycholestan-3-one 3-ethylene Ketal (Catalyzed by Ketone 2)

Example 17

5β,6β-Epoxycholestan-3-one 3-ethylene Ketal (Catalyzed by Ketone 4)

Example 18

5β,6β-Epoxy-17β-hydroxyandrost-5-en-3-one 3-ethylene Ketal (Catalyzed by Ketone 2)

Example 19

5β,6β-Epoxy-17β-hydroxyandrost-5-en-3-one 3-ethylene Ketal (Catalyzed by Ketone 4)

Example 20

5β,6β-Epoxy-17β-acetoxyandrost-5-en-3-one 3-ethylene Ketal (Catalyzed by Ketone 2)

Example 21

5β,6β-Epoxy-17β-acetoxyandrost-5-en-3-one 3-ethylene Ketal (Catalyzed by Ketone 4)

Example 22

5β,6β-Epoxy-17β-acetoxyandrost-5-en-3-one 3-ethylene Ketal (Catalyzed by Ketone 4)

Example 23

5β,6β-Epoxy-17β-acetoxyandrost-5-en-3-one 3-ethylene Ketal (Catalyzed by Ketone 4)

Example 24

5β,6β-Epoxy-17β-acetoxyandrost-5-en-3-one 3-ethylene Ketal (Catalyzed by Ketone 4)

Example 25

5β,6β-Epoxy-17β-acetoxyandrost-5-en-3-one 3-ethylene Ketal (Catalyzed by Ketone 4)

Example 26

5β,6β-Epoxy-17β-acetoxyandrost-5-en-3-one 3-ethylene Ketal (Catalyzed by Ketone 4)

Example 27

5β,6β-Epoxy-17β-acetoxyandrost-5-en-3-one 3-ethylene Ketal (Catalyzed by Ketone 4)

Example 28

5β,6β-Epoxy-17β-acetoxyandrost-5-en-3-one 3-ethylene Ketal (Catalyzed by Ketone 4)
Example 29
5β,6β-Epoxy-11α-acetoxypregnene-3,20-dione 3-dieneethylene Ketal (Catalyzed by Ketone 4)

[0176] Following the procedure of Example 1 above, 11α-acetoxy-5-pregnen-3,20-dione 3-ethylene ketal was epoxidized to 5β,6β-epoxy-11α-acetoxypregnene-3,20-dione 3-dieneethylene ketal.

Example 30
5β,6β-Epoxycholestan-3α-ol (catalyzed by Ketone 1)

[0177] Following the procedure of Example 2 above, epi-cholesterol was epoxidized to 5β,6β-epoxycholestan-3α-ol.

Example 31
5β,6β-Epoxyandrosten-3,17-dione 3,17-dieneethylene Ketal (Catalyzed by Ketone 4)

[0178] Following the procedure of Example 1 above, 5-cholene-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxyandrosten-3,17-dione 3,17-dieneethylene ketal.

Example 32
5β,6β-Epoxycholestan-3-one 3-ethylene Ketal (Catalyzed by Ketone 4)

[0179] Following the procedure of Example 5 above, 5-cholene-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxycholestan-3-one 3-ethylene ketal.

Example 33
5β,6β-Epoxy-17β-acetoxyandrost-5-en-3-one 3-ethylene Ketal (Catalyzed by Ketone 4)

[0180] Following the procedure of Example 5 above, 17β-acetoxyandrost-5-en-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxy-17β-acetoxyandrost-3-one 3-ethylene ketal.

Example 34
5β,6β-Epoxypregnene-3,20-dione 3-ethylene Ketal (Catalyzed by Ketone 2)

[0181] Following the procedure of Example 3 above, 5-pregnen-3,20-dione 3-ethylene ketal was epoxidized to 5β,6β-epoxypregnene-3,20-dione 3-ethylene ketal.

Example 35
5β,6β-Epoxypregnene-3,20-dione 3-ethylene Ketal (Catalyzed by Ketone 4)

[0182] Following the procedure of Example 1 above, 5-pregnen-3,20-dione 3-ethylene ketal was epoxidized to 5β,6β-epoxypregnene-3,20-dione 3-ethylene ketal.

Example 36
5β,6β-Epoxypregnene-3,20-dione 3,20-dieneethylene Ketal (Catalyzed by Ketone 4)

[0183] Following the procedure of Example 5 above, 5-pregnen-3,20-dione 3,20-dieneethylene ketal was epoxidized to 5β,6β-epoxypregnene-3,20-dione 3,20-dieneethylene ketal.

Example 37
5β,6β-Epoxy-11α-hydoxypregnene-3,20-dione 3,20-dieneethylene Ketal (Catalyzed by Ketone 4)


Example 38
5β,6β-Epoxy-11α-hydoxypregnene-3,20-dione 3,20-dieneethylene Ketal (Catalyzed by Ketone 2)


Example 39
5β,6β-Epoxy-11α-hydoxypregnene-3,20-dione 3,20-dieneethylene Ketal (Catalyzed by Ketone 4)


Example 40
5β,6β-Epoxy-11α-acetoxypregnene-3,20-dione 3,20-dieneethylene Ketal (Catalyzed by Ketone 2)


Example 41
5β,6β-Epoxy-11α-acetoxypregnene-3,20-dione 3,20-dieneethylene Ketal (Catalyzed by Ketone 4)


[0189] The invention has been described with reference to preferred embodiments. Those skilled in the art will perceive improvements, changes and modifications. Such improvements, changes and modifications are intended to be within the scope of the claims.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Stereoselective epoxidation of 3β-substituted Δ²-steroids by diazirines generated in situ.</th>
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<tbody>
<tr>
<td>entry</td>
<td>ketone catalyst</td>
</tr>
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<td>1</td>
<td>1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>2&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> βα-epoxide ratio is determined by NMR analysis.
TABLE 1-continued

<table>
<thead>
<tr>
<th>entry</th>
<th>ketone</th>
<th>catalyst</th>
<th>loading (equivalent)</th>
<th>substrate</th>
<th>reaction time (h)</th>
<th>yield</th>
<th>βα-epoxide (%)</th>
<th>ratio&lt;sup&gt;α&lt;/sup&gt;</th>
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<tr>
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<td>4</td>
<td>6</td>
<td>0.2</td>
<td>20</td>
<td>9</td>
<td>91</td>
<td>10.4/1</td>
<td></td>
</tr>
<tr>
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<td></td>
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<td></td>
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<td>(1/3.9)</td>
<td></td>
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<td>(1/3.4)</td>
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<td>9&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>83</td>
<td>8.5/1</td>
<td>1 (1/3.7)</td>
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</tr>
</tbody>
</table>

<sup>a</sup>Unless otherwise indicated, reaction conditions were as follows: room temperature, 0.3 mmol of substrate, indicated amount of ketone, 1.5 mmol of Oxone<sup>®</sup>, 4.65 mmol of NaHCO<sub>3</sub>, 9 mL of dimethyloxime (DMMM), 3 mL of CH<sub>3</sub>CN, and 6 mL of aqueous Na<sub>2</sub>EDTA solution (4 x 10<sup>-3</sup> M).

<sup>b</sup>Time for complete epoxidation as shown by TLC.

<sup>c</sup>Isolated yield.

<sup>d</sup>The ratio of βα-epoxides was determined by <sup>1</sup>H NMR spectroscopy (500 or 300 MHz).

<sup>e</sup>The value in parentheses was the ratio of βα-epoxides obtained with mCPBA as the oxidant.

<sup>f</sup>The epoxidation reaction was carried out at 0-1°C.

<sup>g</sup>On a 10 mmol scale.

Note: An additional experiment was performed using ketone 4 and substrate 9 in which the catalyst loading and reaction time were 0.2 and 12 h, respectively. The subsequent epoxidation reaction resulted in an 89% yield and a βα-epoxide ratio of 11.4/1.

[0190]

[0191]

TABLE 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>substrate</th>
<th>catalyst loading (equivalent)</th>
<th>reaction time (h)</th>
<th>yield</th>
<th>βα-epoxide (%)</th>
<th>ratio&lt;sup&gt;α&lt;/sup&gt;</th>
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<td>&gt;99:1:1</td>
<td>(1:1)</td>
</tr>
<tr>
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<td>&gt;99:1:1</td>
<td>(1:1)</td>
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<tr>
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<td>&gt;99:1:1</td>
<td>(1:1)</td>
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<td>(1:1)</td>
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<tr>
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<td>91</td>
<td>43:1:1</td>
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</tr>
</tbody>
</table>

<sup>a</sup>Unless otherwise indicated, reaction conditions were as follows: room temperature, 0.3 mmol of substrate, indicated amount of ketone, 1.5 mmol of Oxone<sup>®</sup>, 4.65 mmol of NaHCO<sub>3</sub>, 9 mL of dimethyloxime (DMMM), 3 mL of CH<sub>3</sub>CN, and 6 mL of aqueous Na<sub>2</sub>EDTA solution (4 x 10<sup>-3</sup> M).

<sup>b</sup>Time for complete epoxidation as shown by TLC.

<sup>c</sup>Isolated yield.

<sup>d</sup>The ratio of βα-epoxides was determined by <sup>1</sup>H NMR spectroscopy (500 or 300 MHz).

<sup>e</sup>The value in parentheses was the ratio of βα-epoxides obtained with mCPBA as the oxidant.

<sup>f</sup>In another run, the ratio of βα-epoxides was >99:1 with acetone and water (3:1) as solvents.

What is claimed is:

1. A method of producing mostly ββββββ-epoxides of steroids from Δ^-unsaturated steroids by an epoxidation reaction using a ketone and an oxidizing agent under conditions effective to generate epoxides.

wherein said ketone is selected from compounds of generic formula I.
R₁ or R₂ in formula (I) is selected from alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOR (where R=H, alkyl or aryl), OCOOR (where R=H alkyl or aryl), OCOCH₃R₂ (where R= alkyl or aryl), OCONR₂R₃, (where R₁ or R₂=H, alkyl or aryl), OSiR₂R₃ (where R₁ or R₂=alkyl or aryl), and halogen;
R₁ or R₂ in formula (I) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOR (where R=alkyl or aryl), OCOOR (where R=alkyl or aryl), OCOCH₃R₂ (where R=aryl), OCONR₂R₃, (where R₁ or R₂=H, alkyl or aryl), OSiR₂R₃ (where R₁, R₂ or R₃=alkyl or aryl), and halogen;
R₂, R₃, R₄, and R₅ in formula (I) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR₂R₃ (where R₁ or R₂=H, alkyl or aryl);
R₆ or R₇ in formula (I) is selected from alkyl, halogenated alkyl, and alkyl; and
A in formula (I) is selected from halogen, OTf, BF₄, OAc, NO₂, BPh₄, PF₆, and SbF₆.

2. The method of claim 1 wherein said oxidizing reagent is selected from the group consisting of potassium peroxomonosulfate, sodium hypochlorite, sodium perborate, hydrogen peroxide, and peracids.

3. The method of claim 2 wherein said epoxidation reaction is carried out using potassium peroxomonosulfate as an oxidizing agent.

4. The method of claim 1 wherein said epoxidation reaction is carried out in a homogeneous solvent system containing dimethoxymethane-acetonitrile-water, acetonitrile-water, acetone-water, dioxane-water, dimethoxyethane-water, tetrahydrofuran-water, or a biphasic solvent system containing dichloromethane-water, chloroform-water, benzene-water, toluene-water, dimethoxymethane-water, or dichlylether-water, or mixtures thereof.

5. The method of claim 1 wherein said epoxidation reaction is carried out at a temperature within the range from about -10°C. to about 40°C.
6. The method of claim 5 wherein said epoxidation reaction is carried out at room temperature.
7. The method of claim 1 wherein said epoxidation reaction is carried out at a pH within the range from about 7.0 to about 12.0.
8. The method of claim 7 wherein said pH is within the range from about 7.0 to about 7.5.
9. The method of claim 7 wherein said pH is controlled by using a pH-stat or a buffer.
10. The method of claim 9 wherein said buffer is selected from the solutions consisting of sodium bicarbonate, sodium carbonate, sodium borate, sodium hydrogen phosphate, sodium dihydrogen phosphate, potassium hydrogen phosphate, potassium dihydrogen phosphate, potassium bicarbonate, potassium carbonate, potassium hydroxide, or mixtures thereof.

11. The method of claim 1 wherein said epoxidation reaction provides said epoxides in at least about 5:1 β/α-epoxide ratio.

12. A method of producing mostly β,6α-epoxides of steroids from Δ⁴-unsaturated steroids having a substituent at the 3β-position by an epoxidation reaction using a ketone and an oxidizing agent under conditions effective to generate epoxides.

13. The method of claim 12 wherein said substituent is selected from OR (where R=H, alkyl or aryl), O(CH₂)₃OR (where n=1, 2 or 3, R=H, alkyl or aryl), O(CH₂)ₙSO₃R (where n=1, 2 or 3, n=0, 1 or 2; R=H, alkyl or aryl), OSiR₂R₃ (where R₁, R₂, or R₃=alkyl or aryl), OSO₃R (where n=0, 1 or 2; R=H, alkyl or aryl), OCO₂R (where n=1 or 2; R=H, alkyl or aryl), OCONR₂R₃ (where R₁, R₂, R₃=alkyl or aryl), OPO₃R (where n=2 or 3, R=alkyl or aryl), NR₂R₅ (where R₁, R₂=H, alkyl or aryl), NR₄CO₂R₃ (where n=1 or 2; R₁ or R₂=H, alkyl or aryl), NR₅CO₂R₃ (where n=1 or 2; R₁, R₂, R₃=H, alkyl or aryl), NR₅SO₃R₂ (where n=1 or 2; R₁=H, alkyl or aryl, R₂=alkyl or aryl), NPh₃ (Ph=phenyl group), NR₂R₅ (where R₁, R₂, R₃=H, alkyl or aryl), SiR₂R₅ (where R₁, R₂, R₃=H, alkyl or aryl), SO₃R (where n=0, 1 or 2; R=H, alkyl or aryl), SO₃R₂ (where n=1 or 2; R=H, alkyl or aryl), halogen, CN, NO₂, alkyl, ary, COOR (where R=H, alkyl or aryl), and CONR₂R₃ (where R₁ or R₂=H, alkyl or aryl).

14. The method of claim 12 wherein said Δ⁴-unsaturated steroid having a substituent at the 3α-position is selected from the group consisting of Δ⁴-unsaturated steroids having a ketal derivative of ketone group or a thioether derivative of ketone group at the 3-position.

15. The method of claim 12 wherein said ketone is selected from the group consisting of compounds of generic formula II, III, IV, and V wherein...
X in formula (III) is selected from (CR_3R_4)_n (where n=1, 2, 3, 4, or 5; R_3 or R_4=H, alkyl or aryl), O, S, SO, SO_2, and NR (where R=H, alkyl or aryl);

R_12, R_16, R_17, or R_20 in formula (III) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOR (where R=H, alkyl or aryl), OCOOR (where R=alkyl or aryl), OCONR, OR (where R_1 or R_2=H, alkyl or aryl), OSIR, RO_2R_3 (where R_1, R_2 or R_3=alkyl or aryl), and halogen;

R_12, R_16, R_17, or R_20 in formula (III) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR, R_2 (where R_2=H, alkyl or aryl);

R_16 or R_20 in formula (IV) is selected from alkyl, halogenated alkyl, aryl, CR, OR, OCOR (where R_1, R_2 or R_3=H, alkyl or aryl), CR, OR, COOR (where R_1 or R_2=H, alkyl or aryl), CR, OR, COOR (where R_1, R_2 or R_3=H, alkyl or aryl), CR, OR, COOR (where R_1, R_2, or R_3=H, alkyl or aryl), and CR, OR, SO_2R_3 (where R_1, R_2, or R_3=H, alkyl or aryl); and

Y in formula (V) is selected from H, alkyl, halogenated alkyl, aryl, NO_2, CN, F, Cl, Br, I, COOR (where R=H or alkyl), OR (where R=H, alkyl or aryl), OSO_2R (where R=H, alkyl or aryl), OSOR (where R=H, alkyl or aryl), SO_2R (where R=H, alkyl or aryl), SO_3R (where R=H, alkyl or aryl), SOON R_1R_2 (where R_1=H, alkyl or aryl), NR SOOR_2 (where R=H, alkyl or aryl; R_2=alkyl or aryl), NR SOR (where R=H, alkyl or aryl; R_2=alkyl or aryl), CR, R_3OR (where R_1, R_2 or R_3=H, alkyl or aryl), CR, (OR)_2, (where R=H or alkyl; R_2=alkyl), CF_3, CF_2CF_3, OTF, OI, OCOR (where R=H, alkyl or aryl), and OSIR, R_3R_5 (where R_1, R_2 or R_3=alkyl or aryl).

16. The method of claim 12 wherein said epoxidation reaction is carried out in a homogeneous solvent system containing dimethoxyxylene-acetonitril-water, acetonitrile-water, acetonitrile-water, acetonitrile-water, dimethoxyethanewater, tetrahydrofuran-water, or a biphasic solvent system containing dichloromethane-water, chloroform-water, benzene-water, toluene-water, dimethoxyxylene-water, or dichloroethane-water, or mixtures thereof.

17. The method of claim 12 wherein said oxidizing reagent is selected from the group consisting of potassium peroxomonosulfate, sodium hypochlorite, sodium perborate, hydrogen peroxide, and peracids.

18. The method of claim 17 wherein said epoxidation reaction is carried out using potassium peroxomonosulfate as an oxidizing agent.

19. The method of claim 12 wherein said epoxidation reaction is carried out at a temperature within the range from about -10°C to about 40°C.

20. The method of claim 19 wherein said epoxidation reaction is carried out at room temperature.

21. The method of claim 12 wherein said epoxidation reaction is carried out at a pH within the range from 7.0 to about 12.0.

22. The method of claim 21 wherein said pH is within the range from about 7.0 to about 7.5.

23. The method of claim 21 wherein said pH is controlled by using a pH-stat or a buffer.

24. The method of claim 23 wherein said buffer is selected from the solutions consisting of sodium bicarbonate, sodium carbonate, sodium borate, sodium hydrogencarbonate, sodium dihydrogencarbonate, sodium hydroxide, potassium hydrogencarbonate, potassium dihydrogencarbonate, potassium bicarbonate, and potassium carbonate, potassium hydroxide, and mixtures thereof.

25. The method of claim 12 wherein said epoxidation reaction provides said epoxides in at least about 5:1 β/α-epoxide ratio.

26. A method of producing mostly 5β,6α-epoxides of steroids from Δ^3-unsaturated steroids by an epoxidation reaction using a dioxirane under conditions effective to generate epoxides,

wherein said dioxirane is selected from compounds of generic formula VI,
R₁ or R₂ in formula (VI) is selected from alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOR (where R=H, alkyl or aryl), OCOOR (where R=alkyl or aryl), OCOOCH₃R (where R=aryl), OCONR₂ (where R₁ or R₂=H, alkyl or aryl), OSIR₂R₃ (where R₁, R₂ or R₃=alkyl or aryl), and halogen;

R₂ or R₃ in formula (VI) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOR (where R=H, alkyl or aryl), OCOOR (where R=alkyl or aryl), OCOOCH₃R (where R=aryl), OCONR₂ (where R₁ or R₂=H, alkyl or aryl), OSIR₂R₃ (where R₁, R₂ or R₃=alkyl or aryl), and halogen;

R₀, R₁, R₂, or R₃ in formula (VI) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONIR₂ (where R₁ or R₂=H, alkyl or aryl);

R₀ or R₁₀ in formula (VI) is selected from alkyl, halogenated alkyl, aryl, and alkyl; and

A in formula (VI) is selected from halogen, OTf, BF₄⁻, OAc, NO₂, BPh₄⁻, PF₆⁻, and SBF₆⁻.

27. The method of claim 26 wherein said dioxirane is generated in situ from a ketone and an oxidizing agent selected from potassium peroxydisulfate, sodium hypochlorite, sodium perborate, hydrogen peroxide, and peracids.

wherein said ketone is selected from compounds of generic formula I,

![Generic Formula I](image)

28. The method of claim 26 wherein said epoxidation reaction is carried out in a solvent selected from acetonitrile, dimethoxymethane, acetone, dioxane, dimethoxyethane, tetrahydrofuran, dichloromethane, chloroform, benzene, toluene, diethyl ether, water, and mixtures thereof.

29. The method of claim 26 wherein said epoxidation reaction is carried out at a temperature within the range from about –40°C to about 40°C.

30. The method of claim 26 wherein said epoxidation reaction is carried out at a pH within the range from about 7.0 to about 12.0.

31. The method of claim 26 wherein said epoxidation reaction provides said epoxides in at least about 5:1 βα-epoxide ratio.

32. A method of producing mostly 5β,6α-epoxides of steroids from Δ⁴-un saturated steroids having a substituent at the 3α-position by an epoxidation reaction using a dioxirane under conditions effective to generate epoxides.

33. The method of claim 22 wherein said substituent is selected from OR (where R=H, alkyl or aryl), O(CH₂)ₙOR (where n=1, 2 or 3, R=H, alkyl or aryl), O(CH₂)ₙSO₃R (where n=1, 2 or 3, R=H, alkyl or aryl), OCONR₂R₃ (where R₁, R₂ or R₃=alkyl or aryl), OSIR₂R₃ (where R₁, R₂ or R₃=alkyl or aryl), OCOOCH₃R (where R=aryl), OCONR₂ (where R₁ or R₂=H, alkyl or aryl), OSIR₂R₃ (where R₁, R₂ or R₃=alkyl or aryl), and halogen.

34. The method of claim 22 wherein said Δ⁴-un saturated steroid having a substituent at the 3α-position is selected from the group consisting of Δ⁴-un saturated steroids having a ketal derivative of ketone group or a thiketal derivative of ketone group at the 3-position.

35. The method of claim 22 wherein said dioxirane is selected from the group consisting of compounds of generic formula VII, VIII, IX, and X.
R₁, R₂, R₃, or R₄ in formula (VII) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOR (where R=H, alkyl or aryl), OCOOR (where R=alkyl or aryl), OCOOCH₂R (where R=ary), OCONR₂R₃ (where R₁ or R₂=H, alkyl or aryl), OSiR₂R₃ (where R₁ or R₂=alkyl or aryl), and halogen;

R₅, R₆, R₇, R₈, R₉, or R₁₀ in formula (VII) is selected from H, alkyl, halogenated alkyl, ary1, COOR (where R=H, alkyl or aryl), and CONR₂R₃ (where R₁ or R₂=H, alkyl or aryl); A in formula (VII) is selected from halogen, OTf, BF₄, OAc, NO₂, BPh₄, PF₆, and SbF₆;

X in formula (VIII) is selected from (CR₂)ₐ₋₅ (where m=1, 2, 3, 4, or 5; R₁ or R₂=H, alkyl or aryl), O, S, SO₂, and NR (where R=H, alkyl or aryl);

R₁₁, R₁₂, R₁₃, or R₁₄ in formula (VIII) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOR (where R=H, alkyl or aryl), OCOOR (where R=alkyl or aryl), OCOOCH₂R (where R=ary), OCONR₂R₃ (where R₁ or R₂=H, alkyl or aryl), OSiR₂R₃ (where R₁ or R₂=alkyl or aryl), and halogen;

R₁₅, R₁₆, R₁₇, or R₁₈ in formula (VIII) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR₂R₃ (where R₁ or R₂=H, alkyl or aryl);

Y in formula (X) is selected from H, alkyl, halogenated alkyl, aryl, NO₂, CN, F, Cl, Br, I, COOR (where R=H or alkyl), OR (where R=H, alkyl or aryl), OSO₂R (where R=H, alkyl or aryl), OSO₃R (where R=H, alkyl or aryl), OSO₃R (where R=H, alkyl or aryl), SO₂R (where R=H, alkyl or aryl), OSO₂R (where R=H, alkyl or aryl), SO₂R (where R=H, alkyl or aryl), SO₃R (where R=H, alkyl or aryl), SO₃R (where R=H, alkyl or aryl), SO₃R (where R=H, alkyl or aryl), SO₃R (where R=H, alkyl or aryl), SO₃R (where R=H, alkyl or aryl), SO₃R (where R=H, alkyl or aryl), SO₃R (where R=H, alkyl or aryl), SO₃R (where R=H, alkyl or aryl), and OSiR₂R₃ (where R₁ or R₂=alkyl or aryl).

36. The method of claim 32 wherein said dioxirane is generated in situ from a ketone and an oxidizing agent selected from potassium peroxydisulfate, sodium hypochlorite, sodium perborate, hydrogen peroxide, and peracids.

37. The method of claim 36 wherein said ketone is selected from the group consisting of compounds of generic formula II, III, IV, and V,
A in formula (II) is selected from halogen, OTf, BF₄⁻, OAc, NO₂, BPh₄⁻, PF₆⁻, and SbF₆⁻.

X in formula (III) is selected from (CR₂)ₙ (where n=1, 2, 3, 4, or 5; R₁ or R₂=H, alkyl or aryl), O, S, SO, SO₂, and NR (where R=H, alkyl or aryl);

R₁₁, R₁₂, R₁₅, or R₁₄ in formula (III) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOOR (where R=H, alkyl or aryl), OCOOR (where R=alkyl or aryl), OCOOR, OCONR₂ (where R₁ or R₂=H, alkyl or aryl), OSiR₃R₂ (where R₁, R₂ or R₃=alkyl or aryl), and halogen;

R₁₅, R₁₆, R₁₇, or R₁₈ in formula (III) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR₂R₂ (where R₁ or R₂=H, alkyl or aryl);

R₁₆ or R₂₀ in formula (IV) is selected from alkyl, halogenated alkyl, aryl, CR₂, OCOOR (where R₁, R₂ or R₃=H, alkyl or aryl), CR₂OCOOR (where R₁ or R₂=H, alkyl or aryl; R₃=alkyl or aryl), CR₂NR₂, COOR (where R₁, R₂ or R₃=H, alkyl or aryl; R₄=alkyl or aryl), CR₂NR, SO₂R₂ (where R₁, R₂ or R₃=H, alkyl or aryl; R₄=alkyl or aryl); and

Y in formula (V) is selected from H, alkyl, halogenated alkyl, aryl, NO₂, CN, F, Cl, Br, I, COOR (where R=H or alkyl), OR (where R=H, alkyl or aryl), OSO₂R (where R=H, alkyl or aryl), OSO₂R (where R=H, alkyl or aryl), SO₂R (where R=H, alkyl or aryl), SO₃R (where R=H, alkyl or aryl), SO₃R (where R=H, alkyl or aryl), SO₃R (where R=H, alkyl or aryl), NO₂, NR₂, OR₂ (where R₁ or R₂=H, alkyl or aryl), NR₂SO₂R (where R₁=H, alkyl or aryl; R₂=alkyl or aryl), NR₂SO₂R (where R₁=H, alkyl or aryl; R₂=alkyl or aryl), CR₂OR₂ (where R₁ or R₂=H, alkyl or aryl), CR₂(OR₂) (where R₁ or R₂=H or alkyl; R₃=alkyl), CF₃, CF₂CF₃, OTf, OMe, OCOOR (where R=H, alkyl or aryl), and OSiR₂R₂R (where R₁, R₂ or R₃=alkyl or aryl).

38. The method of claim 32 wherein said epoxidation reaction is carried out in a solvent selected from acetone, dimethoxyethane, acetone, dioxane, dimethoxyethane, tetrahydrofuran, dichloromethane, chloroform, benzene, toluene, diethyl ether, water, and mixtures thereof.

39. The method of claim 32 wherein said epoxidation reaction is carried out at a temperature within the range from about -40°C to about 40°C.

40. The method of claim 32 wherein said epoxidation reaction is carried out at a pH within the range from about 7.0 to about 12.0.

41. The method of claim 32 wherein said epoxidation reaction provides said epoxides in at least about 5:1 β/α-epoxide ratio.

42. A method comprising:

producing mostly 5β,6β-epoxides of steroids by epoxidation reactions of Δ⁵-un saturated steroids of generic formula XI catalyzed by ketones of generic formula XII, wherein

R₁ in formula (XI) is selected from H, OR (where R=H or alkyl), OCH₂CH₃, OCOOR (where R=alkyl or aryl), OSiR₂R₂R₂ (where R₁, R₂ or R₃=alkyl or aryl); halogen, CN, alkyl, aryl, and COOR (where R=H, alkyl or aryl);

R₂ in formula (XI) is selected from H, OR (where R=H or alkyl), COOR (where R=alkyl or aryl), OCH₂CH₃, halogen, CF₃, and CF₂CF₃;

R₃ and R₄ in formula (XI) are each selected from the group consisting of H, alkyl, aryl, halogen, OR (where R=H or alkyl), OCOOR (where R=alkyl or aryl), OSiR₂R₂R₂ (where R₁, R₂ or R₃=alkyl or aryl), COOR (where R=alkyl), OCH₂OR (where R=H or alkyl), COCH₂OCOR (where R=alkyl or aryl), COCH₂F, COOR (where R=H or alkyl), COO(CH₂CH₃)OR (where R=alkyl), COO(CH₂CH₃)CH₂OR (where R=H or alkyl), COO(CH₂CH₃)CH₂OCOR (where R=alkyl or aryl), and COO(CH₂CH₃)COCH₂F; or, are selected from the group consisting of O, OCH₂CH₂O, and OCH₂CH₂CH₂O;
R₄ in formula (XI) is selected from H, C₃-C₆ alkyl, halogen, OR (where R=H or alkyl), OCOR (where R=alkyl or aryl), and OSiR₃'R₅'R₆' (where R₃', R₅', or R₆'=alkyl or aryl);

R₅ in formula (XI) is selected from H, C₃-C₆ alkyl, halogen, OR (where R=H or alkyl), OCOR (where R=alkyl or aryl), and OSiR₃'R₅'R₆' (where R₃', R₅', or R₆'=alkyl or aryl);

R₆ in formula (XI) is selected from H, halogen, OR (where R=H or alkyl), and OCOR (where R=alkyl or aryl);

R₇ in formula (XI) is selected from H, halogen, OR (where R=H or alkyl), and OCOR (where R=alkyl or aryl);

R₁₄ and R₂₀ in formula (XII) are each selected from alkyl and aryl;

R₁₅ and R₁₆ in formula (XII) are each selected from H, alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR₂ (where R₁ or R₂=H, alkyl or aryl);

A in formula (XII) is selected from OTf, BF₄, OAc, NO₃, BF₃·OEt, PF₅, and SbF₆.

43. The method of claim 42 wherein C₃-C₆ alkyl is selected from the group consisting of methyl, ethyl, normal-propyl, iso-propyl, normal-butyl, iso-butyl, sec-butyl, and tert-butyl; and said aryl is selected from the group consisting of phenyl, substituted phenyl, naphthyl, and substituted naphthyl groups.

44. The method of claim 42 wherein said epoxidation reactions are carried out in a homogeneous solvent system selected from the group consisting of dimethoxyethane-water, acetonitrile-water, acetone-water, dioxane-water, dimethoxyethane-water, tetrahydrofuran-water, and mixtures thereof.

45. The method of claim 42 wherein said epoxidation reactions are carried out in a biphasic solvent system selected from the group consisting of dichloromethane-water, chloroform-water, benzene-water, toluene-water, dimethoxyethane-water, or diethylene-water, and mixtures thereof.

46. The method of claim 42 wherein said oxidizing reagent is selected from the group consisting of potassium peroxydisulfate, sodium hypochlorite, sodium perborate, hydrogen peroxide, and peracids.

47. The method of claim 42 wherein said epoxidation reactions are carried out at a temperature within the range from about -10° C. to about 40° C.

48. The method of claim 47 wherein said epoxidation reactions are carried out at room temperature.

49. The method of claim 42 wherein said epoxidation reactions are carried out at a pH within the range from about 7.0 to about 12.0.

50. The method of claim 49 wherein said pH is within the range from 7.0 to 7.5.

51. The method of claim 49 wherein said pH is controlled by using a pH-stat or a buffer.

52. The method of claim 51 wherein said buffer is selected from the group consisting of sodium bicarbonate, sodium carbonate, sodium borate, sodium hydroxide, potassium hydroxide, sodium dihydrogenphosphate, potassium dihydrogenphosphate, potassium bicarbonate, potassium carbonate, potassium hydroxide, or mixtures thereof.

53. A method comprising:

producing mostly 5β,6β-epoxides of steroids by epoxidation reactions of Δ²-ununsaturated steroids of generic formula XIII catalyzed by ketones of generic formula XIV, XV, XVI, and XVII, wherein

X₁ in formula (XIII) is selected from the group consisting of H, OR (where R=H or alkyl), OCH₂CH₂O, OCOR (where R=alkyl or aryl), OSiR₃'R₅'R₆' (where R₃', R₅', or R₆'=alkyl or aryl), halogen, CN, alkyl, aryl, and COOR (where R=H, alkyl or aryl), and,

X₂ in formula (XIII) is selected from the group consisting of OR (where R=H or alkyl), OCH₂CH₂O, OCOR (where R=alkyl or aryl), OSiR₃'R₅'R₆' (where R₃', R₅', or R₆'=alkyl or aryl), halogen, CN, NO₂, alkyl, and aryl; or,

X₃ and X₄ in formula (XIII) are each selected from the group consisting of O, OCH₂CH₂O, and OCH₂CH₂CH₂O;

R₈ in formula (XIII) is selected from H, OR (where R=H or alkyl), OCH₂CH₂O, OCOR (where R=alkyl or aryl), OSiR₃'R₅'R₆' (where R₃', R₅', or R₆'=alkyl or aryl), halogen, CN, alkyl, aryl, and COOR (where R=H, alkyl or aryl), and,

R₉ and R₁₀ in formula (XIII) are each selected from the group consisting of H, alkyl, aryl, halogen, OR (where R=H or alkyl), OCOR (where R=alkyl or aryl), OSiR₃'R₅'R₆' (where R₃', R₅', or R₆'=alkyl or aryl), COCH₂OR (where R=H or alkyl), COCH₂OCOR (where R=alkyl or aryl), COCH₂F, COOR (where R=H or alkyl), COCH₂CH₂O (where R=alkyl), COCH₂CH₂OH (where R=H or alkyl), COCH₂CH₂OCH₂OR (where R=alkyl or aryl), and COCH₂CH₂OCH₂F; or R₉ and R₁₀ in formula (XIII) are each selected from the group consisting of O, OCH₂CH₂O, and OCH₂CH₂CH₂O.
$R_{12}$ and $R_{13}$ in formula (XIII) are each selected from the group consisting of $H$, $C_1-C_4$ alkyl, halogen, OR (where $R=H$ or alkyl), OCOR (where $R=alkyl$ or aryl), and OSiR$_3$R$_3'$. ($R$, $R'=R''=alkyl$ or aryl);

$R_{13}$ and $R_{14}$ in formula (XIII) are each selected from the group consisting of $H$, halogen, OR (where $R=H$ or alkyl), and OCOR (where $R=alkyl$ or aryl);

$R_{15}$ or $R_{16}$ in formula (XIV) is selected from alkyl and aryl;

$R_{17}$ or $R_{18}$ in formula (XIV) is selected from $H$, alkyl, aryl, COOR (where $R=H$, alkyl or aryl), and CONR$_2$R$_2$ (where $R$ or $R'=H$, alkyl or aryl);

$R_{19}$ or $R_{20}$ in formula (XIV) is selected from $H$, $C_1-C_4$ alkyl, halogenated alkyl, and halogen; and

$A$ in formula (XIV) is selected from OTf, BF$_4$, OAc, NO$_2$, BPh$_4$, PF$_6$, and SbF$_6$;

$R_{21}$ or $R_{22}$ in formula (XV) is selected from $H$, alkyl, aryl, COOR (where $R=H$, alkyl or aryl), and CONR$_2$R$_2$ (where $R$ or $R'=H$, alkyl or aryl);

$Y$ in formula (XV) is selected from CH$_2$, O, S, SO, SO$_2$, and NR (where $R=H$ or alkyl);

$R_{23}$ or $R_{24}$ in formula (XV) is selected from $H$, alkyl, aryl, COOR (where $R=H$, alkyl or aryl), and CONR$_2$R$_2$ (where $R$ or $R'=H$, alkyl or aryl);

$R_{25}$ or $R_{26}$ in formula (XV) is selected from $H$, halogen, $C_1-C_4$ alkyl, halogenated alkyl, and OCOR (where $R=alkyl$ or aryl);

$R_{27}$ or $R_{28}$ in formula (XVI) is selected from $C_1-C_4$ alkyl, halogenated alkyl, CH$_2$OCOR (where $R=alkyl$ or aryl), and

$Z$ in formula (XVII) is selected from $H$, $C_1-C_4$ alkyl, aryl, NO$_2$, CN, F, Cl, Br, I, COOR (where $R=alkyl$), CH$_2$OR (where $R=H$ or alkyl), CH(OR)$_2$ (where $R=alkyl$), CF$_3$, CF$_2$CF$_3$, OTf, OTs, OCOR (where $R=alkyl$ or aryl), and OSiR$_3$R$_3'$ (where $R$, $R'=alkyl$ or aryl)

54. The method of claim 53 wherein said $C_1-C_4$ alkyl is selected from the group consisting of methyl, ethyl, normal-propyl, iso-propyl, normal-butyl, iso-butyl, sec-butyl, and tert-butyl; and said aryl selected from the group consisting of phenyl, substituted phenyl, napthyl, and substituted naphthyl groups.

55. The method of claim 53 wherein said epoxidation reactions are carried out in a homogeneous solvent system selected from the group consisting of dimethoxyacetonitrile-water, acetonitrile-water, acetone-water, dioxane-water, dimethoxyethane-water, and tetrahydrofuran-water, and mixtures thereof.

56. The method of claim 53 wherein said epoxidation reactions are carried out in a biphasic solvent system selected from the group consisting of dichloromethane-water, chloroform-water, benzene-water, toluene-water, dimethoxyacetonitrile-water, or diethyl ether-water, and mixtures thereof.

57. The method of claim 53 wherein said oxidizing reagent is selected from the group consisting of potassium peroxomonosulfate, sodium hypochlorite, sodium perborate, hydrogen peroxide, and peracids.

58. The method of claim 53 wherein said epoxidation reactions are carried out at a temperature within the range from about -10° C. to about 40° C.

59. The method of claim 58 wherein said epoxidation reactions are carried out at room temperature.

60. The method of claim 53 wherein said epoxidation reactions are carried out at a pH within the range from about 7.0 to about 12.0.

61. The method of claim 60 wherein said pH is within the range from 7.0 to 7.5.

62. The method of claim 60 wherein said pH is controlled by using a pH-stat or a buffer.

63. The method of claim 62 wherein said buffer is selected from the group consisting of sodium bicarbonate, sodium carbonate, sodium borate, sodium hydrogenphosphate, sodium dihydrogenphosphate, sodium hydroxide, potassium hydrogenphosphate, potassium dihydrogenphosphate, potassium bicarbonate, potassium carbonate, potassium hydroxide, or mixtures thereof.

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