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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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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.

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Provisional application No. 60/183,396, filed on Feb. 18, 2000.
KETONES:

1. \( \text{CF}_3 \text{CO} \)
2. \( \text{CO}_2 \)
3. \( \text{PhCO} \text{O} \text{Ph} \)
4. \( \text{PhCO} \text{O} \text{Ph} \text{OTf} \)

STEROIDS:

5. \( \text{CH}_3 \text{C}_8 \text{H}_17 \text{HO} \)
6. \( \text{CH}_3 \text{C}_8 \text{H}_17 \text{HO} \)
7. \( \text{CH}_3 \text{C}_8 \text{H}_17 \text{MeO} \)
8. \( \text{C}_8 \text{H}_17 \text{HO} \)
9. \( \text{CH}_3 \text{C}_8 \text{H}_17 \text{OR} \text{R} = \text{H} \)
10. \( \text{CH}_3 \text{C}_8 \text{H}_17 \text{OR} \text{R} = \text{MOM} \)
11. \( \text{CH}_3 \text{C}_8 \text{H}_17 \text{OR} \text{R} = \text{H} \)
12. \( \text{CH}_3 \text{C}_8 \text{H}_17 \text{OR} \text{R} = \text{Ac} \)
13. \( \text{C}_8 \text{H}_17 \text{OR} \)
14. \( \text{C}_8 \text{H}_17 \text{OR} \)
15. \( \text{CH}_3 \text{C}_8 \text{H}_17 \text{OR} \text{R} = \text{H} \)
16. \( \text{CH}_3 \text{C}_8 \text{H}_17 \text{OR} \text{R} = \text{Ac} \)
17. \( \text{CH}_3 \text{C}_8 \text{H}_17 \text{OR} \text{R} = \text{O} \)
18. \( \text{CH}_3 \text{C}_8 \text{H}_17 \text{OR} \text{R} = \text{OCH}_2 \text{CH}_2 \text{O} \)
19. \( \text{CH}_3 \text{C}_8 \text{H}_17 \text{OR} \text{R} = \text{H} \)
20. \( \text{CH}_3 \text{C}_8 \text{H}_17 \text{OR} \text{R} = \text{Ac} \)

**Fig. 2**
Fig. 5

AUTHENTIC SAMPLES OF 5a/5b

PPM  3.2  3.1  3.0  2.9  2.8  2.7

Fig. 6

TABLE 1, ENTRY 1

PPM  3.2  3.1  3.0  2.9  2.8  2.7
Fig. 11

AUTHENTIC SAMPLES
OF 6a/6b

Fig. 12

TABLE 1, ENTRY 5
Fig. 13

TABLE 1, ENTRY 6

Fig. 14

AUTHENTIC SAMPLES
OF 7a/7b
Fig. 15

TABLE 1, ENTRY 6

Fig. 16

TABLE 1, ENTRY 7
Fig. 17

AUTHENTIC SAMPLES OF 8a/8b

Fig. 18

TABLE 1, ENTRY 7
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. 27

AUTHENTIC SAMPLES OF 11a/11b

Fig. 28

TABLE 2, ENTRY 1
Fig. 39

Table 2, Entry 8

Fig. 40

Table 2, Entry 9
Fig. 47

AUTHENTIC SAMPLES
OF 15a/15b

Fig. 48

TABLE 2, ENTRY 13
Fig. 51

AUTHENTIC SAMPLES
OF 16a/16b

Fig. 52

TABLE 2, ENTRY 15
Fig. 55

AUTHENTIC SAMPLES
OF 17a/17b

Fig. 56

TABLE 2, ENTRY 17

Fig. 57

TABLE 2, ENTRY 18
Fig. 58

TABLE 2, ENTRY 19

Fig. 59

AUTHENTIC SAMPLES
OF 18a/18b
Fig. 64

AUTHENTIC SAMPLES
OF 19a/19b

Fig. 65

TABLE 2, ENTRY 21
METHOD FOR SYNTHESIZING 5BETA, 6BETA-EPOXIDES OF STEROIDS BY A HIGHLY BETASELECTIVE 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 Feb. 18, 2000.

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 oxysterols (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 oxysterols. For example, α- and β-epoxides of cholesterol are auto-oxidation products of cholesterol in vivo, and both are cytotoxic and mutagenic. The isomeric α- and β-epoxides are hydrolysed by cholesterol 5α,6-epoxide hydrolase to cholestane-3β,5α,6β-triol which has potent hypcholesterolemic activity. On the other hand, both epoxides inhibit the cholesterol 7α-hydroxylase which catalyzes the rate-determining step of bile acid synthesis. As 5α,6α-epoxides are readily available via epoxidation of Δ5-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 5β,6β-epoxides and their derivatives because they are difficult to obtain in high selectivity. More importantly, the 5β,6β-epoxy functionality is found in a number of naturally occurring steroids of antitumor activities, e.g., jaborosalactone A, withaferin A, and withanolide D.

[0004] Common organic oxidants such as 3-chloroperbenzoic acid (mCPBA) generally give α-epoxides as the major products for epoxidation of 3β-substituted Δ5-steroids and show poor selectivities for epoxidation of 3α-substituted Δ5-steroids except epi-cholesterol. This is because peracid epoxidation follows a concerted pathway via spiro transition states (α-TS and β-TS (TS=transition state); see FIG. 1). The β-TS suffers from steric interactions between the peracid and the C(10) angular methyl group for epoxidation of 3β-substituted Δ5-steroids, while both the β-TS and the α-TS encounter similar steric hindrance for epoxidation of 3α-substituted Δ5-steroids. Dioxiranes are new-generation reagents for oxidation under mild and neutral conditions. Unfortunately, poor selectivities were reported in epoxidation of 3β-substituted Δ5-steroids by either isolated or in situ generated dioxiranes. While dioxiranes also epoxidize olefins through a spiro TS, their steric environment is different from that of peracids. To minimize steric interactions, dioxiranes prefer to approach the C(5)==C(6) double bond of Δ5-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 α-substituents of dioxiranes and the 3α and 4β substituents of steroids that determine the facial selectivity of epoxidation.


[0006] Cicala, G., et al., J. Org. Chem., 1982, vol. 47, pages 2670-2673, disclose the epoxidation of a Δ5-unsaturated steroid that is not a 3α-substituted Δ5-unsaturated steroid, and in which the ketone catalyst is acetone.

[0007] Marples, B. A., et al. Tetrahedron Lett., 1991, vol. 32, pages 553-556, disclose the epoxidation reactions of four Δ5-unsaturated steroids that are not 3α-substituted Δ5-unsaturated steroids, and using a variety of ketones. In these reactions either no epoxide was observed, or the β/α-epoxide ratio was about 1:1.


SUMMARY OF THE INVENTION

[0012] In accordance with the invention, a method is provided for producing mostly 5β,6β-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.

[0013] A wide range of Δ5-unsaturated steroids, bearing different functional groups such as hydroxy, carbonyl, acetyl or ketal group, as well as different side chains, are converted to the corresponding synthetically and biologically interesting 5β,6β-epoxides with excellent β-selectivities and high yields.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] FIG. 1 is a diagrammatic representation of the general epoxidation reaction between Δ5-unsaturated steroids 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 5b,6b-epoxides of steroids and 5a,6a-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 Δ4-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 Δ4-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 5b,6b-epoxides of steroids from Δ4-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,

![Chemical Structure](image)

in which R1 or R4 in formula (I) is selected from alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOOR (where R=alkyl or aryl), OCOCH2R (where R=aryl), OCONOR2, R5 (where R1 or R2=H, alkyl or aryl), OSiR3R6 (where R1, R2 or R3=alkyl or aryl), and halogen;

R2 or R3 in formula (I) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOOR (where R=alkyl or aryl), OCOCH2R (where R=aryl), OCONOR2, R5 (where R1 or R2=H, alkyl or aryl), OSiR3R6 (where R1, R2 or R3=alkyl or aryl), and halogen;

R2 or R3 in formula (I) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), and CONOR2 (where R1, R2 or R3=H, alkyl or aryl);

R2 or R3 in formula (I) is selected from alkyl, halogenated alkyl, and aryl; and

A in formula (I) is selected from halogen, OTf, BF4, OAc, NO3, BPh4, PF6, and SbF6;

In another aspect of the invention, a method of producing mostly 5β,6β-epoxides of steroids from Δ4-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)nSO2R (where n=1, 2 or 3; n=0, 1, or 2; R=H, alkyl or aryl), OSiR3R6R7 (where R1, R2 or R3=alkyl or aryl), OSO2R (where R=0, 1, or 2; R=H, alkyl or aryl), OCO2R (where n=1 or 2; R=H, alkyl or aryl), CONOR2 (where R1 or R2=H, alkyl or aryl), OPO2R (where n=2 or 3; R=alkyl or aryl), NR2R3 (where R1 or R2=H, alkyl or aryl), NRCONR2R3 (where R1, R2 or R3=H, alkyl or aryl), NR2SO2R3 (where n=1 or 2; R=H, alkyl or aryl), PF6 (Ph=phthaloyl group), N,N,N,N,N-Pentamethylenediamine, HCl, H2SO4, HNO3, HBr, HClO4, Cl2, SO2Cl2, SO3, SOCl2, SB2O3, SF6, and halogen.

Further in accordance with this aspect of the invention, the Δ4-unsaturated steroid having a substituent at the 3α-position can be selected from the group consisting of Δ4-unsaturated steroids having a ketone group or a thioacetate derivative of ketone group at the 3-position.

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

![Chemical Structure](image)

in which 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), OCONOR2, R5 (where R1 or R2=H, alkyl or aryl), OSiR3R6 (where R1, R2 or R3=alkyl or aryl), and halogen;

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), OCONOR2, R5 (where R1 or R2=H, alkyl or aryl), OSiR3R6 (where R1, R2 or R3=alkyl or aryl), and halogen;

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), OCONOR2, R5 (where R1 or R2=H, alkyl or aryl), OSiR3R6 (where R1, R2 or R3=alkyl or aryl), and halogen;

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), OCONOR2, R5 (where R1 or R2=H, alkyl or aryl), OSiR3R6 (where R1, R2 or R3=alkyl or aryl), and halogen;

A in formula (I) is selected from halogen, OTf, BF4, OAc, NO3, BPh4, PF6, and SbF6;
[0031] X in formula (III) is selected from (CR,R2)n (where n=1, 2, 3, 4, or 5; R1 or R2=alkyl or aryl), O, S, SO2, and NR (where R=H, alkyl or aryl);

[0032] R14, R16, R17, or R18 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,R (where R1 or R2=H, alkyl or aryl), OSOR,R,R3 (where R1, R2 or R3=alkyl or aryl), and halogen;

[0033] R19, R19, R20, or R21 in formula (III) is selected from H, alkyl, halogenated alkyl, aryi, COOR (where R=H, alkyl or aryl), and CONR,R2 (where R1 or R2=H, alkyl or aryl);

[0034] R11 or R20 in formula (IV) is selected from alkyl, halogenated alkyl, aryl, CR,R2OCOR (where R1, R2 or R3=H, alkyl or aryl), CR,R2OCOOR (where R1 or R2=H, alkyl or aryl; R3=alkyl or aryl), CR,R2NR2COOR (where R1, R2 or R3=H, alkyl or aryl; R4=alkyl or aryl), CR,R2NR2COR (where R1, R2, R3 or R4=alkyl or aryl), and CR,R2NR2SO2R (where R1, R2 or R3=H, alkyl or aryl; R4=alkyl or aryl), and

[0035] Y in formula (V) is selected from H, alkyl, halogenated alkyl, aryl, NO2, CN, F, Cl, Br, I, COOR (where R=H or aryl), OR (where R=H, alkyl or aryl), OSO2R (where R=H, alkyl or aryl), OSOR (where R=H, alkyl or aryl), SOR (where R=H, alkyl or aryl), SO2R (where R=H, alkyl or aryl), SO3R (where R=H, alkyl or aryl), and

[0036] 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), OCOOR (where R=H, alkyl or aryl), OCOOR (where R=alkyl or aryl), OCOCHR (where R=ary1), OCONR,R (where R1 or R2=H, alkyl or aryl), OSOR,R2R3 (where R1, R2 or R3=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=H, alkyl or aryl), OCOCHR (where R=ary1), OCONR,R2 (where R1 or R2=H, alkyl or aryl), OSOR,R2R3 (where R1, R2 or R3=alkyl or aryl), and halogen;

[0039] R5, R5, R6, or R8 in formula (VI) 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);

[0040] R9 or R20 in formula (VI) is selected from alkyl, halogenated alkyl, and aryl; and

[0041] A in formula (VI) is selected from halogen, OTf, BF4, OAc, NO3, BPb4, 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.
[0043] R₁ or R₄ 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), OOCOCHR₆ (where R=H, aryl or alkyl), OCONR₂R₅ (where R₁ or R₄=H, alkyl or aryl), OSiR₂R₅ (where R₁, R₂ or R₄=alkyl or aryl), and halogen;

[0044] R₂ or R₅ in formula (I) is selected from H, alkyl, halogenated alkyl, alkyl, OR (where R=H, alkyl or aryl), OCOOR (where R=H, alkyl or aryl), OCOCH₂R₆ (where R=H, aryl or alkyl), OCONR₂R₅ (where R₁ or R₄=H, alkyl or aryl), OSiR₂R₅ (where R₁, R₂ or R₄=alkyl or aryl), and halogen;

[0045] R₃, R₆, R₇, or R₈ in formula (I) is selected from H, alkyl, halogenated alkyl, alkyl, OR (where R=H, alkyl or aryl), and CONR₂R₅ (where R₂ or R₄=H, alkyl or aryl);

[0046] R₉ or R₁₀ in formula (I) is selected from alkyl, halogenated alkyl, and aryl; and

[0047] A in formula (I) is selected from halogen, OTf, BF₃, OAc, NO₃, BPh₃, PF₅, and SbF₅.

[0048] In yet another aspect of the invention, a method of producing mostly 5β,6β-epoxides of steroids from Δ₅-unsaturated steroids having a substituent at the 3α-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 3α-position can be 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)ₙSO₂R (where n=1, 2 or 3; n=0, 1 or 2; R=H, alkyl or aryl), OSiR₂R₅ (where R₁, R₂ or R₄=alkyl or aryl), OSO₂R (where n=0, 1 or 2; R=H, alkyl or aryl), OCOOR (where n=1 or 2; R=H, alkyl or aryl), OCONR₂R₅ (where R₁ or R₄=H, alkyl or aryl), OPO₃R (where n=2 or 3; R=alkyl or aryl), NR₂R₄ (where R₁ or R₄=H, alkyl or aryl), NR₂CO₂R₅ (where n=1 or 2; R₁ or R₄=H, alkyl or aryl), NR₂CONR₂R₅ (where R₁, R₂ or R₄=H, alkyl or aryl), NR₂SO₂R₂ (where n=1 or 2; R₁ or R₄=H, alkyl or aryl), R₃=alkyl or aryl), NPhth (Phth=phthaloyl group), *NR₂R₄ (where R₁, R₂ or R₄=H, alkyl or aryl), SiR₂R₅ (where R₁, R₂ or R₄=H, alkyl or aryl), SO₂R (where n=0, 1 or 2; R=H, alkyl or aryl), SCOR (where n=1 or 2; R=H, alkyl or aryl), halogen, CN, NO₂, alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR₂R₅ (where R₁ or R₄=H, alkyl or aryl).

[0049] Further in accordance with this aspect of the invention, the Δ₅-unsaturated steroid having a substituent at the 3α-position can be selected from the group consisting of Δ₅-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] 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), OOCOCHR₆ (where R=H, aryl or alkyl), OCONR₂R₅ (where R₁ or R₄=H, alkyl or aryl), OSiR₂R₅ (where R₁, R₂ or R₄=alkyl or aryl), and halogen;

[0052] R₁, R₂, R₃, R₅, R₆, or R₇ in formula (VII) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOOR (where R=H, alkyl or aryl), OCONR₂R₅ (where R₁ or R₄=H, alkyl or aryl), OSiR₂R₅ (where R₁, R₂ or R₄=alkyl or aryl), and halogen;

[0053] A in formula (VII) is selected from halogen, OTf, BF₃, OAc, NO₃, BPh₃, PF₅, and SbF₅;

[0054] X in formula (VIII) is selected from (CR₃)₉, (where n=1, 2, 3, 4, or 5; R₁ or R₄=H, alkyl or aryl), O, S, SO₂, and NR (where R=H, alkyl or aryl);

[0055] R₁₃, R₁₄, R₁₅, or R₁₆ in formula (VIII) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOOR (where R=H, alkyl or aryl), OCONR₂R₅ (where R₁ or R₄=H, alkyl or aryl), OCOCHR₆ (where R=H, aryl or alkyl), OCONR₂R₅ (where R₁ or R₄=H, alkyl or aryl), and halogen;

[0056] R₁₃, R₁₄, R₁₅, or R₁₆ in formula (VIII) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR₂R₅ (where R₁ or R₄=H, alkyl or aryl);

[0057] R₁₉ or R₂₀ in formula (IX) is selected from alkyl, halogenated alkyl, aryl, CR₃R₂OCOR₃ (where R₁, R₂ or R₄=H, alkyl or aryl), CR₃R₂OCOOR₃ (where R₁ or R₄=H,
alkyl or aryl; R₁=alkyl or aryl), CR₂NR₃COOR₄ (where R₁, R₂ or R₃=H, alkyl or aryl, R₄=alkyl or aryl), CR₂NR₃COR₄ (where R₁, R₂ or R₃=H, alkyl or aryl), CR₂NR₃SO₂R₄ (where R₁, R₂ or R₃=H, alkyl or aryl; R₄=alkyl or aryl); and

[0062] A in formula (II) is selected from halogen, OTf, BFe₄, OAc, NO₂, BPh₄, PF₆, and SbF₆;

[0063] X in formula (III) is selected from (CR₂R₃)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);

[0064] R₁, R₂, R₃, or R₄ 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), OCOCH₃ (where R=H, alkyl or aryl), OCONR₂ (where R₁, R₂=H, alkyl or aryl), OCONOR₂ (where R₁, R₂=H, alkyl or aryl), OCONOR₂ (where R₁, R₂=H, alkyl or aryl), OCONOR₂ (where R₁, R₂=H, alkyl or aryl), and halogen;

[0065] R₅, R₆, R₇, or R₈ in formula (III) is selected from H, alkyl, halogenated alkyl, aryl, OCONR₂ (where R₁, R₂=H, alkyl or aryl), OCONOR₂ (where R₁, R₂=H, alkyl or aryl), OCONOR₂ (where R₁, R₂=H, alkyl or aryl), OCONOR₂ (where R₁, R₂=H, alkyl or aryl), OCONOR₂ (where R₁, R₂=H, alkyl or aryl), and halogen;

[0066] R₁ or R₂ in formula (IV) is selected from alkyl, halogenated alkyl, aryl, CR₂NR₃COOR₄ (where R₁, R₂=H, alkyl or aryl), CR₂NR₃COOR₄ (where R₁, R₂=H, alkyl or aryl), CR₂NR₃COOR₄ (where R₁, R₂=H, alkyl or aryl), CR₂NR₃COOR₄ (where R₁, R₂=H, alkyl or aryl), CR₂NR₃COOR₄ (where R₁, R₂=H, alkyl or aryl), and halogen;

[0067] 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 or alkyl), OCOOR (where R=H or alkyl), OCOCH₃ (where R=H, alkyl or aryl), OCONR₂ (where R₁, R₂=H, alkyl or aryl), OCONOR₂ (where R₁, R₂=H, alkyl or aryl), OCONOR₂ (where R₁, R₂=H, alkyl or aryl), OCONOR₂ (where R₁, R₂=H, alkyl or aryl), and halogen;

[0068] 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. In such embodiments of the invention, the ketone can be selected from the group consisting of compounds of generic formula II, III, IV, and V:

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=H, alkyl or aryl), OCOCH₃ (where R=H, alkyl or aryl), OCONR₂ (where R₁, R₂=H, alkyl or aryl), OCONOR₂ (where R₁, R₂=H, alkyl or aryl), and halogen;

R₅, R₆, R₇, or R₈ in formula (II) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONNR₂ (where R₁ or R₂=H, alkyl or aryl); and
alkyl or aryl), SO₃R (where R=H, alkyl or aryl), SO₂R₂ (where R₁, or R₂=H, alkyl or aryl), NR₃,SO₃R₂ (where R₁=H, alkyl or aryl; R₂=alkyl or aryl), NR₃,SO₃R₂ (where R₁=H, alkyl or aryl; R₂=alkyl or aryl), CR₃,OR₄ (where R₁, R₂, or R₃=H, alkyl or aryl), CR₃,OR₄ (where R₁=H or alkyl; R₂=alkyl), CF₃, CF₃,CF₃, OTf, OTs, OCOR (where R=H, alkyl or aryl), and OSiR₃R₄R₅ (where R₁, R₂ or R₅=alkyl or aryl).

[0068] Epoxidation reactions in accordance with the invention and using dioxiranes can be carried out in a solvent selected from acetone, dimethoxyethane, acetone, dioxane, dimethoxyethane, tetrahydrofuran, dichloromethane, chloroform, benzene, toluene, diethyl ether, water and mixtures thereof.

[0069] In accordance with one embodiment of the invention herein, a method of producing mostly 5,6,6'-epoxides of steroids comprises epoxidation reactions of Δ⁴-unsaturated steroids of generic formula XI catalyzed by ketones of generic formula XII, wherein

\[ \text{XI} \]

[0070] X₁ in formula (XI) is selected from H, OR (where R=H or alkyl), OCH₃, OCH₂CH₃, OCOR (where R=alkyl or aryl), OSiR₃R₄R₅ (where R₁, R₂ or R₃=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=H or alkyl), OCH₂CH₃, halogen, CF₃, and CF₂CF₃; 

[0072] R₂ and R₃ in formula (XI) are each selected from the group consisting of H, alkyl, halogen, OR (where R=H or alkyl), OCH₂CH₃, OCOR (where R=alkyl or aryl), OSiR₃R₄R₅ (where R₁, R₂ or R₃=alkyl or aryl), COCH₃, COCH₂OR (where R=H or alkyl), COCH₂COR (where R=alkyl or aryl), COCL₂F, COOR (where R=H or alkyl), C(OCH₃)₂OH (where R=alkyl), C(OCH₃)₂CH₂OR (where R=H or alkyl), C(OCH₃)₂CH₂COR (where R=alkyl or aryl), and C(OCH₃)₂CH₂CF₃; or, are selected from the group consisting of O, OCH₂CH₂O, and OCH₂CH₂CH₂O;

[0073] R₄ in formula (XI) is selected from H, C₃H₇, alkyl, halogen, OR (where R=H or alkyl), OCH₃, OCOR (where R=alkyl or aryl), and OSiR₃R₄R₅ (where R₁, R₂ or R₃=alkyl or aryl); 

[0074] R₅ in formula (XI) is selected from H, C₃H₇, alkyl, halogen, OR (where R=H or alkyl), OCH₃, OCOR (where R=alkyl or aryl), and OSiR₃R₄R₅ (where R₁, R₂ or R₃=alkyl or aryl); 

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

[0076] R₂ in formula (XI) is selected from H, halogen, OR (where R=H or alkyl), and OCOOR (where R=alkyl or aryl); 

[0077] R₁₃ and R₁₇ in formula (XII) are each selected from alkyl and aryl; 

[0078] R₁₇ and R₁₈ 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); 

[0079] R₁₉ and R₂₀ in formula (XII) are each selected from C₃H₇, alkyl, halogenated alkyl, and halogen;

[0080] A in formula (XII) is selected from OTf, BF₄, OAc, NO₂, BPh₃, PF₃, and SbF₅.

[0081] In another embodiment of the present invention, a method of producing mostly 5,6,6'-epoxides of steroids comprises epoxidation reactions of Δ⁴-unsaturated steroids of generic formula XIII catalyzed by ketones of generic formula XIV, XV, XVI, and XVII, wherein

\[ \text{XIII} \]

[0082] X₁ in formula (XIII) is selected from the group consisting of H, OR (where R=H or alkyl), OCH₃, OCOOR (where R=alkyl or aryl), OSiR₃R₄R₅ (where R₁, R₂ or R₃=alkyl or aryl), halogen, CN, alkyl, aryl, and COOR (where R=H, alkyl or aryl), and;

[0083] X₁ in formula (XIII) is selected from the group consisting of OR (where R=H or alkyl), OCH₃, OCOOR (where R=alkyl or aryl), OSiR₃R₄R₅ (where R₁, R₂ or R₃=alkyl or aryl), halogen, CN, alkyl, aryl, and COOR (where R=H, alkyl or aryl), and;

[0084] X₁ and X₁ in formula (XIII) are each selected from the group consisting of O, OCH₃, OCH₂CH₂O, and OCH₂CH₂CH₂O;

[0085] R₉ in formula (XIII) is selected from H, OR (where R=H or alkyl), OCH₃, OCOOR (where R=alkyl or aryl), OCH₂CH₃, halogen, CF₃, and CF₂CF₃;

[0086] R₉ in formula (XIII) is selected from the group consisting of H, alkyl, aryl, halogen, OR (where R=H or alkyl), OCOOR (where R=alkyl or aryl), OSiR₃R₄R₅ (where R₁, R₂ or R₃=alkyl or aryl), and COOR (where R=alkyl),
COCH_{12}OR (where R=H or alkyl), COCH_{12}OCOR (where R=alkyl or aryl), COCH_{12}F, COOR (where R=H or alkyl), C(OCH_{12}CH_{12}O)R (where R=alkyl), C(OCH_{12}CH_{12}O)CH_{12}OR (where R=H or alkyl), C(OCH_{12}CH_{12}O)CH_{12}OCOR (where R=alkyl or aryl), and C(OCH_{12}CH_{12}O)CH_{12}F; or R_{12} and R_{13} in formula (XIII) are each selected from the group consisting of O, OCH_{12}CH_{12}O, and OCH_{12}CH_{12}CH_{12}O;

R_{12} and R_{13} in formula (XIII) are each selected from the group consisting of H, C_{12}-C_{14} alkyl, halogen, OR (where R=H or alkyl), COOR (where R=alkyl or aryl), and OsI\_4; R_{12}', R_{13}', R_{14}', R_{15}', R_{16}', R_{17}', R_{18}', R_{19}', R_{20}', R_{21}', R_{22}', R_{23}', R_{24}', R_{25}', and R_{26}' are each alkyl or aryl;

R_{12} or R_{13} in formula (XIV) is each selected from alkyl and aryl;

R_{12}' or R_{13}' in formula (XIV) is each selected from C_{12}-C_{14} alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR_{12}R_{13} (where R_{12} or R_{13}=H, alkyl or aryl);

R_{12} or R_{20} in formula (XIV) is each selected from C_{12}-C_{14} alkyl, halogen, halogenated alkyl, and halogen;

A in formula (XIV) is selected from OTf, BF_{4}, OAc, NO_{3}, 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_{22} or R_{23} in formula (XV) is each selected from C_{12}-C_{14} alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR_{22}R_{23} (where R_{22} or R_{23}=H, alkyl or aryl);

R_{25} or R_{24} in formula (XV) is each selected from C_{12}-C_{14} alkyl, halogenated alkyl, and OCOR (where R=alkyl or aryl); and

Z in formula (XVII) is selected from H, C_{12}-C_{14} 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_{12}'R_{13}'R_{14}' (where R_{12}', R_{13}', R_{14}'=alkyl or aryl);

In each of the disclosed embodiments, C_{12}-C_{14} 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 dimethoxyethane-water, acetone-water, acetone-water, acetone-water, dimethoxyethane-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 dichloromethane-water, chloroform-water, benzene-water, toluene-water, dimethoxyethane-water, and diethylether-water and mixtures thereof.

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

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.
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 hydrogen phosphate, sodium dihydrogen phosphate, sodium hydroxide, potassium hydrogen phosphate, potassium dihydrogen phosphate, potassium bicarbonate, potassium carbonate and potassium hydroxide.

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 C(6) 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 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 epoxidation 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).

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 >49:1, entries 5-24; Table 3). Substrates with 3-ketol 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 >99:1) in 88% yield. These results clearly demonstrate the power of ketone-catalyzed epoxidation method.

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 Δ5β,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 these receptors as well as for drug discovery.

General Experimental

The 1H and 13C NMR spectra (FIGS. 4-70) 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 FTIR 165 Fourier Transform Spectrophotometer. Mass spectra were recorded with a Finningan MAT 95 mass spectrometer for both low resolution and high resolution mass spectra.

Substrates 5, 6, 8, 9, ketone 1, tetrahydrothiopyran-4-one ( 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

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 dimethoxyethane (DMM, 9 mL) and acetonitrile (CH3CN, 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).

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-one (1.7 mg, 0.015 mmol) in dimethoxyethane (DMM, 9 mL) and acetonitrile (CH3CN, 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 MgSO$_4$ and filtered through a pad of silica gel. The ratio of α/β-epoxides was determined by $^1$H 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 (1.37 g, 3 mmol) in dimethoxymethane (DMM, 300 mL) and acetonitrile (CH$_3$CN, 100 mL) at room temperature was added an aqueous Na$_2$EDTA solution (200 mL, 4 x 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 MgSO$_4$ and filtered through a pad of silica gel. The ratio of α/β-epoxides was determined by $^1$H 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 dimethoxymethane (DMM, 300 mL) and acetonitrile (CH$_3$CN, 100 mL) at room temperature was added an aqueous Na$_2$EDTA solution (200 mL, 4 x 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 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 MgSO$_4$ and filtered through a pad of silica gel. The ratio of α/β-epoxides was determined by $^1$H 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).

**[0111]** Sodium bicarbonate (0.4 mmol) and mCPBA (0.2 mmol) were added to a solution of substrate (0.1 mmol) in CH$_2$Cl$_2$ (3 mL). The resulting mixture was stirred at room temperature for 2 h and quenched with a solution of saturated aqueous Na$_2$S$_2$O$_3$. The reaction mixture was diluted with ethyl acetate and washed with a solution of saturated aqueous NaHCO$_3$ and brine. The organic layer was dried over anhydrous MgSO$_4$ and filtered through a pad of silica gel. The product analysis was performed as above.

**Characterization Data for Epoxides**

**[0112]**

![Chemical Structure](image)

**[0113]** 5a and 5b (as a mixture of 1:15.1 ratio; Table 1, Entry 4):

**[0114]** $^1$H NMR (300 MHz, CDCl$_3$) 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), 2.90 (d, J=4.3 Hz, 1/16.1×1H, 6β-H), 1.06 (s, 1/16.1×3H, 19-CH$_3$), 0.99 (s, 15.1/16.1×3H, 19-CH$_3$), 0.89 (d, J=6.6 Hz, 15.1/16.1×3H, 21-CH$_3$), 0.86 (d, J=6.6 Hz, 15.1/16.1×6H, 26-CH$_3$ and 27CH$_3$), 0.64 (s, 15.1/16.1×3H, 18-CH$_3$), 0.61 (s, 1/16.1×3H, 18-CH$_3$); $^1$C NMR of 5b (75.5 MHz, CDCl$_3$) 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.

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

**[0116]** $^1$H NMR (300 MHz, CDCl$_3$) δ 3.95-3.85 (m, 1/11.4×1H, 3α-H), 3.76-3.65 (m, 10/11.4×1H, 3α-H), 3.13
(d, J=2.5 Hz, 10.4/11.4x1H, 6α-H), 2.95 (d, J=4.3 Hz, 1/11.4x1H, 6β-H), 1.09 (s, 1/11.4x3H, 19-CH₃), 1.03 (s, 10.4/11.4x3H, 19-CH₃), 0.85 (s, 10.4/11.4x3H, 18-CH₃), 0.82 (s, 1/11.4x3H, 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 (500 MHz, CDCl₃) δ 8.95-3.84 (m, 1/9.8x1H, 3α-H), 3.74-3.64 (m, 8.8/9.8x1H, 3α-H), 3.60 (t, J=8.5 Hz, 1H, 17α-H), 3.07 (d, J=2.4 Hz, 8.8/9.8x1H, 6α-H), 2.91 (d, J=4.4 Hz, 1/9.8x1H, 6β-H), 1.07 (s, 1/9.8x3H, 19-CH₃), 1.01 (s, 8.8/9.8x3H, 19-CH₃), 0.72 (s, 8.8/9.8x3H, 18-CH₃), 0.69 (s, 1/9.8x3H, 18-CH₃); ¹³C NMR of 8b (75.5 MHz, CDCl₃) δ 81.81, 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, 1/10x1H, 3α-H), 3.34 (s, 3H, OCH₃), 3.28-3.22 (m, 9/10x1H, 3α-H), 3.11 (d, J=2.4 Hz, 9/10x1H, 6α-H), 2.95 (d, J=4.4 Hz, 1/10x1H, 6β-H), 1.18 (s, 9/10x3H, 19-CH₃), 1.17 (s, 1/10x3H, 19-CH₃), 1.02 (s, 9/10x6H, 20-CH₃, and 21-CH₃), 0.87 (s, 9/10x3H, 18-CH₃), 0.85 (s, 1/10x3H, 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, 36.75, 35.54, 32.30, 31.66, 28.93, 27.27, 27.02, 25.95, 21.08, 17.13, 14.08; IR (CH₂Cl₂) 1730 cm⁻¹; LRMS (EI, 20 eV) m/z 346 (100), 314 (15), 123 (31), 108 (22); HRMS (EI, 20 eV) calcd for C₂₂H₂₆O₃ (M⁺): 346.2508, found: 346.2508; Anal. Calcd for C₂₂H₂₆O₃: 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 9.34-3.87 (m, 1/12.6x1H, 3α-H), 3.75-3.65 (m, 11.6/12.6x1H, 3α-H), 3.08 (d, J=2.3 Hz, 11.6/12.6x1H, 6α-H), 2.92 (d, J=4.4 Hz, 11.6/12.6x1H, 6β-H), 2.11 (s, 11.6/12.6x3H, 21-CH₃), 1.06 (s, 1/12.6x3H, 19-CH₃), 1.00 (s, 11.6/12.6x3H, 19-CH₃), 0.59 (s, 11.6/12.6x3H, 18-CH₃), 0.56 (s, 1/12.6x3H, 18-CH₃); ¹³C NMR of 9b (75.5 MHz, CDCl₃) δ 209.48, 69.29, 63.67, 63.50, 62.89, 56.33, 51.19, 43.89, 42.12, 38.84, 34.92, 32.51, 31.46, 30.97, 29.76, 24.36, 22.77, 21.96, 17.07, 13.11.
[0123] 10a and 10b (as a mixture of: 18.5; Table 1, Entry 10).

[0124] \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.73-4.64 (m, 2H, OCH\(_2\)), 3.83-3.74 (m, 1H, 3\(\alpha\)-H), 3.65-3.55 (m, 8.5/9.5x1H, 3\(\alpha\)-H), 3.36 (s, 8.5/9.5x3H, OCH\(_3\)), 3.35 (s, 1H, 9.5x3H, OCH\(_3\)), 3.08 (d, J=2.3 Hz, 8.5/9.5x1H, 6\(\alpha\)-H), 2.91 (d, J=4.3 Hz, 1H, 9.5x1H, 6\(\alpha\)-H), 2.11 (s, 8.5/9.5x3H, 21-CH\(_3\)), 1.06 (s, 1H, 9.5x3H, 19-CH\(_3\)), 1.00 (s, 8.5/9.5x3H, 19-CH\(_3\)), 0.60 (s, 8.5/9.5x3H, 18-CH\(_3\)), 0.56 (s, 1H, 9.5x3H, 18-CH\(_3\)). \(^{13}\)C NMR of 11b (75.5 MHz, CDCl\(_3\)) \(\delta\) 209.35, 94.67, 74.18, 63.67, 63.44, 62.82, 56.33, 55.26, 51.08, 43.88, 39.43, 38.84, 37.07, 35.16, 32.48, 31.45, 29.74, 28.13, 24.35, 22.77, 21.94, 17.07, 13.11; IR (CH\(_3\)Cl) 1700 cm\(^{-1}\); EIMS (20 eV) m/z 376 (100), 314 (90), 133 (60), 95 (33); HRMS (EI, 20 eV) calcd for C\(_{22}\)H\(_{32}\)O\(_4\): M\(^+\) 376.2614, found: 376.2617. Anal. Calcd for C\(_{22}\)H\(_{32}\)O\(_4\): C, 73.37; H, 9.64; Found: C, 73.11; H, 9.68.

[0125] 11b:

[0126] \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.19 (br s, 1H, 3\(\alpha\)-H), 3.07 (d, J=2.0 Hz, 1H, 6\(\alpha\)-H), 0.97 (s, 3H, 19-CH\(_3\)), 0.89 (d, J=6.6 Hz, 3H, 21-CH\(_3\)), 0.86 (d, J=6.0 Hz, 6H, 26-CH\(_2\) and 27-CH\(_3\)), 0.64 (s, 3H, 18-CH\(_3\)). \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 76.03, 63.70, 61.97, 56.31, 56.20, 50.38, 42.31, 39.87, 39.86, 39.49, 36.14, 35.74, 35.53, 33.19, 32.37, 29.82, 28.40, 28.17, 27.99, 24.18, 23.83, 22.81, 22.55, 21.69, 18.07, 17.00, 11.78.

[0127] 11a:

[0128] \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 4.10-4.07 (m, 1H, 3\(\beta\)-H), 2.87 (d, J=4.5 Hz, 1H, 6\(\beta\)-H), 1.04 (s, 3H, 19-CH\(_3\)), 0.89 (d, J=6.6 Hz, 6H, 26-CH\(_2\) and 27-CH\(_3\)), 0.61 (s, 3H, 18-CH\(_3\)). \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 76.02, 65.43, 57.98, 56.38, 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.

[0129] 12b:

[0130] \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.12-5.10 (m, 1H, 3\(\beta\)-H), 3.00 (d, J=2.0 Hz, 1H, 6\(\alpha\)-H), 2.04 (s, 3H, CH\(_3\)COO), 0.99 (s, 3H, 19-CH\(_3\)), 0.89 (d, J=6.6 Hz, 3H, 21-CH\(_3\)), 0.86 (d, J=6.6 Hz, 6H, 26-CH\(_2\) and 27-CH\(_3\)), 0.65 (s, 3H, 18-CH\(_3\)). \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 76.70, 70.50, 63.28, 61.69, 56.33, 56.27, 50.20, 42.34, 39.86, 39.49, 36.63, 36.15, 35.76, 35.43, 33.78, 32.43, 29.81, 28.19, 28.01, 25.47, 24.19, 23.85, 22.82, 22.56, 21.71, 21.34, 18.68, 17.13, 11.78.

[0131] 13b:

[0132] \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 5.97-3.79 (m, 8H, OCH\(_2\)CH\(_3\)), 3.06 (d, J=2.1 Hz, 1H, 6\(\beta\)-H), 1.00 (s, 3H, 19-CH\(_3\)), 0.82 (s, 3H, 18-CH\(_3\)). \(^{13}\)C NMR (75.5 MHz, CDCl\(_3\)) \(\delta\) 119.12, 109.19, 64.97, 64.33, 64.12, 63.94, 62.90,
[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, 6a-H), 0.99 (s, 3H, 19-CH$_3$), 0.89 (d, J=6.7 Hz, 3H, 21-CH$_3$), 0.86 (d, J=6.6 Hz, 6H, 26-CH$_2$ and 27-CH$_2$), 0.64 (s, 3H, 18-CH$_3$). $^{13}$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, 6a-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, 50.79, 50.07, 42.70, 41.45, 36.63, 35.06, 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, 6a-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 81.85, 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, 6a-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 209.41, 109.37, 64.33, 64.16, 63.66, 63.15, 62.95, 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, 6a-H), 1.28 (s, 3H, 21-CH$_3$), 1.00 (s, 3H, 19-CH$_3$), 0.74 (s, 3H, 18-CH$_3$). $^{13}$C NMR (75.5 MHz, CDCl$_3$) δ 81.11, 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.

[0138] 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, 6a-H), 1.28
(s, 3H, 21-CH₃), 1.20 (s, 3H, 19-CH₃), 0.76 (s, 3H, 18-CH₃);

1⁰C NMR (75.5 MHz, CDCl₃) δ 111.47, 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 1³H 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-Epoxysterol-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). To this mixture was added portions 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. 1³H NMR analysis of the product 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-Epoxysterol-3,17-diene 3,17-diethylene ketol (Catalyzed by Ketone 1)

To a solution of 5-androstene-3,17-diene 3,17-diethylene ketol (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 0-1³C, followed by addition of 1,1,1-trifluoroacetone (0.54 mL, 6 mmol). To this solution was added in portions a mixture of Oxone® (922 mg, 1.5 mmol) and sodium bi carbonate (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. 1³H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was >99:1. 5β,6β-Epoxysterol-3,17-diene 3,17-diethylene ketol was obtained after flash column chromatography on silica gel (101 mg, 86% yield).

Example 3

5β,6β-Epoxysterol-3,17-diene 3,17-diethylene Ketol (Catalyzed by Ketone 2)

To a solution of 5-androstene-3,17-diene 3,17-diethylene ketol (112 mg 0.3 mmol) and tetrahydrothiopyran-4-one (1.7 mg, 0.015 mmol) 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 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. 1³H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was 96:1. 5β,6β-Epoxysterol-3,17-diene 3,17-diethylene ketol was obtained after flash column chromatography on silica gel (110 mg, 94% yield).

Example 4

5β,6β-Epoxysterol-3,17-diene 3,17-diethylene Ketol (Catalyzed by Ketone 3)

To a solution of 5-androstene-3,17-diene 3,17-diethylene ketol (112 mg 0.3 mmol) and ketone 3 (9 mg, 0.03 mmol) 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 Oxone® (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. 1³H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was 49:1. 5β,6β-Epoxysterol-3,17-diene 3,17-diethylene ketol was obtained after flash column chromatography on silica gel (109 mg, 93% yield).

Example 5

5β,6β-Epoxysterol-3,17-diene 3,17-diethylene Ketol (Catalyzed by Acetone)

To a solution of 5-androstene-3,17-diene 3,17-diethylene ketol (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 portion 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-Epoxyandrostone-3,17-dione 3,17-diethylene Ketal (Acetone as Catalyst and Co-solvent)

[0153] To a solution of 3-androstone-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 portion 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-one (Catalyzed by Ketone 4)

[0154] To a solution of pregnenolone (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 portion 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-pregnene-3,20-dione 3,20-diethylene 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 portion a mixture of Oxone® (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. ¹H NMR analysis of the crude residue showed that the ratio of β/α-epoxides was >99:1. 5β,6β-Epoxypregnene-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-one (Catalyzed by Ketone 4)

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

Example 10

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

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

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-methoxythiopregn-20-one (Catalyzed by Ketone 4)

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

Example 13

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

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

Example 14

5β,6β-Epoxy-3β-acetoxycholesterol (Catalyzed by Ketone 2)

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

5β,6β-Epoxy-3α-acetoxycholestan (Catalyzed by Ketone 4)

[0162] Following the procedure of Example 1 above, 3α-acetoxycholest-5-one was epoxidized to 5β,6β-epoxy-3α-acetoxycholestone.

Example 16

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

[0163] Following the procedure of Example 3 above, 5-cholesten-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxycholestan-3-one 3-ethylene ketal.

Example 17

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

[0164] Following the procedure of Example 1 above, 5-cholesten-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxycholestan-3-one 3-ethylene ketal.

Example 18

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

[0165] Following the procedure of Example 3 above, 17β-hydroxyandrost-5-en-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxy-17β-hydroxyandrost-5-one 3-ethylene ketal.

Example 19

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

[0166] Following the procedure of Example 1 above, 17β-hydroxyandrost-5-en-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxy-17β-hydroxyandrost-5-one 3-ethylene ketal.

Example 20

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

[0167] Following the procedure of Example 3 above, 17β-acetoxyandrost-5-en-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxy-17β-acetoxyandrost-5-one 3-ethylene ketal.

Example 21

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

[0168] Following the procedure of Example 1 above, 17β-acetoxyandrost-5-en-3-one 3-ethylene ketal was epoxidized to 5β,6β-epoxy-17β-acetoxyandrost-5-one 3-ethylene ketal.

Example 22

5β,6β-Epoxy pregnene-3,20-dione 3,20-dieithylene Ketal (Catalyzed by Ketone 2)

[0169] Following the procedure of Example 3 above, 5-pregene-3,20-dione 3,20-dieithylene ketal was epoxidized to 5β,6β-epoxy pregene-3,20-dione 3,20-dieithylene ketal.

Example 23

5β,6β-Epoxy pregene-3,20-dione 3,20-dieithylene Ketal (Catalyzed by Ketone 4)

[0170] Following the procedure of Example 1 above, 5-pregene-3,20-dione 3,20-dieithylene ketal was epoxidized to 5β,6β-epoxy pregene-3,20-dione 3,20-dieithylene ketal.

Example 24

5β,6β-Epoxy pregene-3,20-dione 3-dieithylene Ketal (Catalyzed by Ketone 2)

[0171] Following the procedure of Example 3 above, 5-pregene-3,20-dione 3-dieithylene ketal was epoxidized to 5β,6β-epoxy pregene-3,20-dione 3-dieithylene ketal.

Example 25

5β,6β-Epoxy pregene-3,20-dione 3-dieithylene Ketal (Catalyzed by Ketone 4)

[0172] Following the procedure of Example 1 above, 5-pregene-3,20-dione 3-dieithylene ketal was epoxidized to 5β,6β-epoxy pregene-3,20-dione 3-dieithylene ketal.

Example 26

5β,6β-Epoxy-11α-hydroxypregene-3,20-dione 3-dieithylene Ketal (Catalyzed by Ketone 2)

[0173] Following the procedure of Example 3 above, 11α-hydroxy-5-pregene-3,20-dione 3-dieithylene ketal was epoxidized to 5β,6β-epoxy-11α-hydroxypregene-3,20-dione 3-dieithylene ketal.

Example 27

5β,6β-Epoxy-11α-hydroxypregene-3,20-dione 3-dieithylene Ketal (Catalyzed by Ketone 4)

[0174] Following the procedure of Example 1 above, 11α-hydroxy-5-pregene-3,20-dione 3-dieithylene ketal was epoxidized to 5β,6β-epoxy-11α-hydroxypregene-3,20-dione 3-dieithylene ketal.

Example 28

5β,6β-Epoxy-11α-acetoxypregene-3,20-dione 3-dieithylene Ketal (Catalyzed by Ketone 2)

[0175] Following the procedure of Example 3 above, 11α-acetoxy-5-pregene-3,20-dione 3-dieithylene ketal was epoxidized to 5β,6β-epoxy-11α-acetoxypregene-3,20-dione 3-dieithylene ketal.
Example 29

5β,6β-Epoxy-11α-acetoxyprogrenene-3,20-dione 3-diene Ethylene Ketal (Catalyzed by Ketone 4)

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

Example 30

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

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

Example 31

5β,6β-Epoxyandrostene-3,17-dione 3,17-diethylene Ketal (Catalyzed by Ketone 4)

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

Example 32

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

[0179] Following the procedure of Example 5 above, 5-cholestene-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-5-en-3-one 3-ethylene ketal.

Example 34

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

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

Example 35

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

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

Example 36

5β,6β-Epoxyprogrenene-3,20-dione 3,20-diethylene Ketal (Catalyzed by Ketone 4)

[0183] Following the procedure of Example 5 above, 5-pregnene-3,20-dione 3,20-diethylene ketal was epoxidized to 5β,6β-epoxyprogrenene-3,20-dione 3,20-diethylene ketal.

Example 37

5β,6β-Epoxy-11α-hydroxyprogrenene-3,20-dione 3,20-diethylene Ketal (Catalyzed by Ketone 4)


Example 38

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


Example 39

5β,6β-Epoxy-11α-hydroxyprogrenene-3,20-dione 3,20-diethylene Ketal (Catalyzed by Ketone 4)


Example 40

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


Example 41

5β,6β-Epoxy-11α-acetoxyprogrenene-3,20-dione 3,20-diethylene Ketal (Catalyzed by Ketone 4)


Example 42

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 1 |

| Stereoselective epoxidation of 3β-substituted A5-steroids by dioxiranes generated in situ* |

<table>
<thead>
<tr>
<th>ketone entry</th>
<th>catalyst</th>
<th>substrate</th>
<th>catalyst loading (equivalents)</th>
<th>reaction time (h)</th>
<th>yield (%)</th>
<th>β′-epoxide fraction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>5</td>
<td>20</td>
<td>1.5</td>
<td>91</td>
<td>1/1.1 (1/4.0)</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>5</td>
<td>0.05</td>
<td>1.5</td>
<td>93</td>
<td>1.1/1</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>5</td>
<td>0.05</td>
<td>3</td>
<td>92</td>
<td>1/1.1</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>5</td>
<td>0.3</td>
<td>16</td>
<td>82</td>
<td>15.1/1</td>
</tr>
<tr>
<td>Entry</td>
<td>Ketone</td>
<td>Substrate</td>
<td>Catalyst Loading (equivalent)</td>
<td>Reaction Time (h)</td>
<td>Yield β/α-Epoxide (%)</td>
<td>Ratio β/α-Epoxide</td>
</tr>
<tr>
<td>-------</td>
<td>--------</td>
<td>-----------</td>
<td>-------------------------------</td>
<td>------------------</td>
<td>------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>6</td>
<td>0.2</td>
<td>9</td>
<td>91</td>
<td>10.4:1</td>
</tr>
<tr>
<td>6</td>
<td>4</td>
<td>7</td>
<td>0.2</td>
<td>20</td>
<td>88</td>
<td>9.0:1 (1/3.1)</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>8</td>
<td>0.2</td>
<td>16</td>
<td>85</td>
<td>8.8:1 (1/3.1)</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>9</td>
<td>0.2</td>
<td>9</td>
<td>93</td>
<td>11.6:1</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>9</td>
<td>0.3</td>
<td>10</td>
<td>86</td>
<td>16.0:1</td>
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<tr>
<td>10</td>
<td>4</td>
<td>10</td>
<td>0.2</td>
<td>20</td>
<td>83</td>
<td>8.5:1 (1/3.7)</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, reaction conditions were as follows: room temperature, 0.3 mmol of substrate, indicated amount of ketone, 1.5 mmol of Oxone®, 4.65 mmol of NaHCO₃, 9 mL of dimethoxymethane (DDM), 3 mL of CH₂CN, and 6 mL of aqueous Na₂EDTA solution (4 × 10⁻⁷ M). *Time for complete epoxidation as shown by TLC. *Isolated yield unless otherwise noted. *The value in parentheses was the ratio of β/α-epoxides obtained with mCPBA as the oxidant. *The yield of β/α-epoxides was determined by 'H NMR spectroscopy (500 or 800 MHz). *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 β/α-epoxide ratio of 11.4:1.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ketone</th>
<th>Substrate</th>
<th>Catalyst Loading (equivalent)</th>
<th>Reaction Time (h)</th>
<th>Yield β/α-Epoxide (%)</th>
<th>Ratio β/α-Epoxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1³</td>
<td>11</td>
<td>20</td>
<td>2</td>
<td>90</td>
<td>3:1 (1:2.5)</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>20</td>
<td>5</td>
<td>94</td>
<td>&gt;99:1</td>
<td>(1:1)</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>20</td>
<td>6</td>
<td>93</td>
<td>&gt;99:1</td>
<td>(1:1)</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>20</td>
<td>6.5</td>
<td>93</td>
<td>&gt;99:1</td>
<td>(1:1)</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>20</td>
<td>6</td>
<td>92</td>
<td>&gt;99:1</td>
<td>(1:1)</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>20</td>
<td>5</td>
<td>91</td>
<td>43:1 (1:1)</td>
<td></td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, reaction conditions were as follows: room temperature, 0.3 mmol of substrate, indicated amount of ketone, 1.5 mmol of Oxone®, 4.65 mmol of NaHCO₃, 9 mL of dimethoxymethane (DDM), 3 mL of CH₂CN, and 6 mL of aqueous Na₂EDTA solution (4 × 10⁻⁷ M). *Time for complete epoxidation as shown by TLC. *Isolated yield unless otherwise noted. *The ratio of β/α-epoxides was determined by 'H NMR spectroscopy (500 or 800 MHz). *The value in parentheses was the ratio of β/α-epoxides obtained with mCPBA as the oxidant. *In another run, the ratio of β/α-epoxides was >99:1 with acetone and water (3:1) as solvents.

**TABLE 3**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Catalyst Loading (equivalent)</th>
<th>Reaction Time (h)</th>
<th>Yield β/α-Epoxide (%)</th>
<th>Ratio β/α-Epoxide</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>11</td>
<td>20</td>
<td>5</td>
<td>90</td>
<td>3:1 (1:2.5)</td>
</tr>
<tr>
<td>2</td>
<td>13</td>
<td>20</td>
<td>5</td>
<td>94</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>3</td>
<td>14</td>
<td>20</td>
<td>6</td>
<td>93</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>20</td>
<td>6.5</td>
<td>93</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>20</td>
<td>6</td>
<td>92</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>20</td>
<td>5</td>
<td>91</td>
<td>43:1 (1:1)</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, reaction conditions were as follows: room temperature, 0.3 mmol of substrate, indicated amount of ketone, 1.5 mmol of Oxone®, 4.65 mmol of NaHCO₃, 9 mL of dimethoxymethane (DDM), 3 mL of CH₂CN, and 6 mL of aqueous Na₂EDTA solution (4 × 10⁻⁷ M). *Time for complete epoxidation as shown by TLC. *Isolated yield unless otherwise noted. *The ratio of β/α-epoxides was determined by 'H NMR spectroscopy (500 or 800 MHz). *The value in parentheses was the ratio of β/α-epoxides obtained with mCPBA as the oxidant. *In another run, the ratio of β/α-epoxides was >99:1 with acetone and water (3:1) as solvents.

**What is claimed is:**

1. A method of producing mostly β,β-epoxides of steroids from Δ¹-unaturated 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 R₄ in formula (I) is selected from alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOOR (where R=H alkyl or aryl), OOCR (where R=H alkyl or aryl), COOH, COOCH₂R₂, (where R₂ is alkyl or aryl), OSI₃R₃, or OSI₂R₄, (where R₃ or R₄=alkyl or aryl), and halogen; 

R₂ or R₃ in formula (I) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), OCOOR (where R=H, alkyl or aryl), OOCR (where R=H alkyl or aryl), OSI₃R₃, OSI₂R₄, (where R₂ or R₃=alkyl or aryl), and halogen; 

R₅, R₆, R₇, R₈, and R₉ in formula (I) 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); 

R₆ or R₇ in formula (I) is selected from alkyl, halogenated alkyl, and aryl; and 

A in formula (I) is selected from halogen, OTf, BF₄, OAc, NO₃, 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 dimethoxyethylene-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, dimethoxyethane-water, or dichylether-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 5β,6α-epoxides of steroids from Δ⁴-unaturated 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(CHO)₂OR (where n=1, 2 or 3, R=H, alkyl or aryl), O(CH₂)ₙSO₂R (where n=1, 2 or 3, n=0, 1 or 2; R=H, alkyl or aryl), OSI₃R₃ (where R₁, R₂ or R₃=alkyl or aryl), OSI₃R₄ (where n=0, 1 or 2; R=H, alkyl or aryl), OCOOCH₂R₂ (where R₁=H, alkyl or aryl), OCOOR (where R₁=H, alkyl or aryl), OSI₃R₃, or OSI₃R₄, (where R₂ or R₃=alkyl or aryl), and halogen; 

R₁, R₂, R₃, R₄, or R₅ in formula (II) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), COOR (where R=H, alkyl or aryl), OOCR (where R=H, alkyl or aryl), OSI₃R₃ or OSI₃R₄ (where R₁ or R₂=alkyl or aryl), and halogen; 

R₂ or R₃ in formula (II) is selected from H, alkyl, halogenated alkyl, aryl, OR (where R=H, alkyl or aryl), COOR (where R=H, alkyl or aryl), OOCR (where R=H, alkyl or aryl), OSI₃R₃ or OSI₃R₄ (where R₁ or R₂=alkyl or aryl), and halogen; 

R₅, R₆, R₇, R₈, or R₉ in formula (II) is selected from H, alkyl, halogenated alkyl, halogenated aryl, COOR (where R=H, alkyl or aryl), and CONR₂R₂ (where R₁ or R₂=H, alkyl or aryl); 

R₆, R₇, or R₈ in formula (II) is selected from alkyl, halogenated alkyl, and aryl; and 

A in formula (II) is selected from halogen, OTf, BF₄, OAc, NO₃, BPh₄, PF₆, and SbF₆. 

14. The method of claim 12 wherein said Δ⁴-unaturated steroid having a substituent at the 3α-position is selected from the group consisting of Δ⁴-unaturated steroids having a ketol derivative of ketone group or a thiolketal 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,R,R), (where n=1, 2, 3, 4, or 5; R or R =H, alkyl or aryl), O, S, SO, SO₂, and NR (where R =H, alkyl or aryl); R₁₁, R₁₂, R₁₃, 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), OCONR,R₂ (where R or R =H, alkyl or aryl), OSIR,R₃ (where R₁, R₂ or R =H, 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 R or R =H, alkyl or aryl);

R₁₉ or R₂₀ in formula (IV) is selected from alkyl, halogenated alkyl, aryl, CR,R₃OCOR₄ (where R₁, R₂ or R =H, alkyl or aryl), CR,R₄OCOR₅ (where R or R =H, alkyl or aryl), CR,R₅OCOR₆ (where R₁, R₂ or R =H, alkyl or aryl), CR,R₆OCOR₇ (where R₁, R₂ or R =H, alkyl or aryl), CR,R₇OCOR₈ (where R₁, R₂ or R =H, alkyl or aryl), CR,R₈OCOR₉ (where R₁, R₂ or R =H, alkyl or aryl), CR,R₉OCOR₁₀ (where R₁, R₂ or R =H, alkyl or aryl), and halogen;

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), OSOR (where R =H, alkyl or aryl), OSOR (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), NR, SOOR (where R =H, alkyl or aryl), NR, SOOR (where R =H, alkyl or aryl), NR, SOOR₁₁ (where R₁, R₂ or R =H, alkyl or aryl), CR,R₄OCOR₅ (where R₁, R₂ or R =H, alkyl or aryl), CR,R₅OCOR₆ (where R₁, R₂, R₃ or R =H, alkyl or aryl), CR,R₆OCOR₇ (where R₁, R₂, R₃ or R =H, alkyl or aryl), CR,R₇OCOR₈ (where R₁, R₂, R₃ or R =H, alkyl or aryl), CR,R₈OCOR₉ (where R₁, R₂, R₃ or R =H, alkyl or aryl), CR,R₉OCOR₁₀ (where R₁, R₂, R₃ or R =H, alkyl or aryl), and halogen.

16. The method of claim 12 wherein said epoxidation reaction is carried out in a homogeneous solvent system containing dimethoxyethane-acetonitrile-water, acetonitrile-water, acetonitrile-water, dimethoxethane-water, tetrahydrofuran-water, or a biphasic solvent system containing dichloromethane-water, chloroform-water, benzene-water, toluene-water, dimethoxyethane-water, or diisyl ether-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 about 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 hydrogenphosphate, sodium dihydrogenphosphate, sodium hydroxide, potassium hydrogenphosphate, potassium dihydrogenphosphate, 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 5α,6α-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), OCOOH₂R (where R=aryl), OCONR₂ (where R₁ or R₂=H, alkyl or aryl), OSiR₃R₅ (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), OCOOH₂R (where R=aryl), OCONR₂ (where R₁ or R₂=H, alkyl or aryl), OSiR₃R₅ (where R₁, R₂ or R₃=alkyl or aryl), and halogen;

R₉, R₁₀, R₄ or R₅ in formula (VI) is selected from H, alkyl, halogenated alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR₂ (where R₁ or R₂=H, alkyl or aryl);

R₉ or R₁₀ in formula (VI) is selected from alkyl, halogenated alkyl, aryl, and halogen; 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 peroxomonosulfate, sodium hypochlorite, sodium perborate, hydrogen peroxide, and peroxyacids.

28. The method of claim 26 wherein said epoxidation reaction is carried out in a solvent selected from acetonitrile, dimethoxyethane, 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 β:α-epoxide ratio.

32. A method of producing mostly β,α-epoxides of steroids from Δ⁴-unsaturated 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 32 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), OSiR₃R₅ (where R₁, R₂ or R₃=alkyl or aryl), OSO₃R (where n=0, 1 or 2; R=H, alkyl or aryl), OCO₂R (where R=H, alkyl or aryl), OPO₃R (where n=2 or 3; R=alkyl or aryl), NR₃ (where R₁, R₂ or R₃=H, alkyl or aryl), NR₃CO₂R₅ (where n=1 or 2; R₁ or R₂=H, alkyl or aryl), NR₃CONR₂ (where R₁, R₂ or R₃=H, alkyl or aryl), NR₃SO₃R₅ (where n=1 or 2; R₁ or R₂=H, alkyl or aryl), NR₃PO₃ (where n=2 or 3; R=alkyl or aryl), NPh₂ (Ph=phenyl group), NR₃R₃R₅ (where R₁, R₂ or R₃=H, alkyl or aryl), SiR₃R₅ (where R₁ or R₂ or R₃=H, alkyl or aryl), SO₃R (where n=0, 1 or 2; R=H, alkyl or aryl), SO₃R (where n=1 or 2; R=H, alkyl or aryl), halogen, CN, NO₂, alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR₂ (where R₁ or R₂=H, alkyl or aryl).

34. The method of claim 32 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 thiol-ketal derivative of ketone group at the 3-position.

35. The method of claim 32 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), OCOOH₂R (where R=aryl), OCONR₂R₃ (where R₁ or R₂=H, alkyl or aryl), OSiR₂R₃ (where R₁, R₂, or R₃=alkyl or aryl), and halogen;

R₅, R₆, R₇, R₈, R₉, or R₁₀ in formula (VII) 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);

A in formula (VII) is selected from halogen, OTf, BF₄, OAc, NO₂, BPh₄, PF₆, and SbF₆;

X in formula (VIII) is selected from (CR₂R₂)ₙ (where n=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), OCOOH₂R (where R=aryl), OCONR₂R₃ (where R₁ or R₂=H, alkyl or aryl), OSiR₂R₃ (where R₁, R₂, or R₃=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);

R₁₉, R₂₀ in formula (IX) is selected from alkyl, halogenated alkyl, aryl, CR₂R₂OCOR₃ (where R₁, R₂ or R₃=H, alkyl or aryl), CR₂R₂OCOOR₃ (where R₁ or R₂=H, alkyl or aryl), R₂=alkyl or aryl), CR₂R₂NR₂COOR₄ (where R₁, R₂, or R₃=H, alkyl or aryl, R₂=alkyl or aryl), CR₂R₂NR₂COR₄ (where R₁, R₂, or R₃=H, alkyl or aryl), CR₂R₂NR₂SO₂R₂ (where R₁, R₂, or R₃=H, alkyl or aryl, R₂=alkyl or aryl); and

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), OSOR (where R=H, alkyl or aryl), OSOR (where R=H, alkyl or aryl), OCONR₂R₃ (where R₁ or R₂=H, alkyl or aryl), OSO₂R (where R=H, alkyl or aryl), SO₂R (where R=H, alkyl or aryl), SO₂R (where R=H, alkyl or aryl), SO₂R (where R=H, alkyl or aryl), NR, SOOR₂ (where R₁=H, alkyl or aryl; R₂=alkyl or aryl), NR, SOOR₂ (where R₁=H, alkyl or aryl; R₂=alkyl or aryl), CR₂OR₂ (where R₁, R₂=H, alkyl or aryl), CR₂OR₂ (where R₁, R₂=H, alkyl or aryl), CF₃, CF₂CF₃, OTf, OTf, OCOOR (where R=H, alkyl or aryl), and OSiR₂R₃R₄ (where R₁, R₂, R₃, or R₄=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 peroxomonosulfate, 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 (CR₅R₆)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, R₁₃, 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), OCOOC₄H₉ (where R=aryl), OCONR₃R₄ (where R₁ or R₂=H, alkyl or aryl), OSiR₃R₄R₅ (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 CONR₃R₄ (where R₁ or R₂=H, alkyl or aryl);

R₁₉ or R₂₀ in formula (IV) is selected from alkyl, halogenated alkyl, aryl, CR₅R₆OCOR₇ (where R₁, R₂ or R₃=H, alkyl or aryl), CR₅R₆OCOCR₇ (where R₁ or R₂=H, alkyl or aryl; R₃=alkyl or aryl), CR₅R₆NRCOCR₇ (where R₁, R₂ or R₃=H, alkyl or aryl; R₄=alkyl or aryl), CR₅R₆NR₂SO₃R₇ (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), 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), NR₂SO₃R (where R₁, R₂=H, alkyl or aryl; R₃=alkyl or aryl), NR₂SO₃R (where R₁, R₂=H, alkyl or aryl; R₃=alkyl or aryl), NR₂SO₃R (where R₁, R₂=H, alkyl or aryl; R₃=alkyl or aryl), CR₅R₆OR (where R₁ or R₂=H, alkyl or aryl), CR₅R₆OR (where R₁ or R₂=H, alkyl or aryl), CR₅(OR)₂ (where R₁ or R₂=H, alkyl or aryl), CF₃, CF₂CF₃, OTf, OTf₈, OCOM (where R=H, alkyl or aryl), and OSiR₃R₄R₅ (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 acetonitrile, dimethoxy methane, acetone, dioxane, dimethoxy ethane, 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-unaturated steroids of generic formula XI catalyzed by ketones of generic formula XII, wherein

X, in formula (XI) is selected from H, OR (where R=H or alkyl), OCH₂CH₃, OCOM (where R=alkyl or aryl), OSiR₃R₄R₅ (where R₁, R₂ or R₃=alkyl or aryl), halogen, CN, alkyl, aryl, and COOR (where R=H, alkyl or aryl);

R₁, in formula (XI) is selected from H, OR (where R=H or alkyl), OCOM (where R=alkyl or aryl), OCH₂CH₃, halogen, CF₃, and CF₂CF₃;

R₂ and R₃ in formula (XI) are each selected from the group consisting of H, alkyl, aryl, halogen, OR (where R=H or alkyl), OCOM (where R=alkyl or aryl), OSiR₃R₄R₅ (where R₁, R₂ or R₃=alkyl or aryl), COR (where R=alkyl), COCH₂OR (where R=H or alkyl), COCH₂OR (where R=alkyl or aryl), COCH₂OR (where R=alkyl or aryl), COCH₂OR (where R=alkyl or aryl), COCH₂OR (where R=alkyl or aryl), COCH₂OR (where R=alkyl or aryl), COCH₂OR (where R=alkyl or aryl), COCH₂OR (where R=alkyl or aryl), COCH₂OR (where R=alkyl or aryl), COCH₂OR (where R=alkyl or aryl), COCH₂OR (where R=alkyl or aryl), COCH₂OR (where R=alkyl or aryl), COCH₂OR (where R=alkyl or aryl), and COCH₂OR (where R=alkyl or aryl), and are selected from the group consisting of O, OCH₂CH₂O, and OCH₂CH₂CH₂O;
R₄ in formula (XI) is selected from H, Cₓ₋₄, alkyl, halogen, OR (where R=H or alkyl), OCOR (where R=alkyl or aryl), and OSiRₓ'₆Rₓ₅Rₓ₃ (where Rₓ', Rₓ₅' or Rₓ₃'=alkyl or aryl);

R₅ in formula (XI) is selected from H, Cₓ₋₄, alkyl, halogen, OR (where R=H or alkyl), OCOR (where R=alkyl or aryl), and OSiRₓ'₆Rₓ₅Rₓ₃ (where Rₓ', Rₓ₅' or Rₓ₃'=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);

R₁₆ and R₁₇ in formula (XII) are each selected from alkyl and aryl;

R₁₈ and R₁₉ in formula (XII) are each selected from H, alkyl, aryl, COOR (where R=H, alkyl or aryl), and CONR₂ (where R, or R=H, alkyl or aryl);

R₂₀ and R₂₁ in formula (XII) are each selected from Cₓ₋₄, alkyl, haloenated alkyl, and halogen; and

A in formula (XII) is selected from OTs, BF₄, OAc, NO₃, BPh₃, PF₆, and SbF₆.  

43. The method of claim 42 wherein Cₓ₋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 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 dimethylformamide-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, dimethylformamide-water, or diethyl ether-water, and mixtures thereof.

46. The method of claim 42 wherein said oxidizing reagent is selected from the group consisting of potassium peroxomonsulfate, 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 hydrogenphosphate, sodium dihydrogenphosphate, sodium hydroxide, potassium hydrogenphosphate, potassium dihydrogenphosphate, potassium bicarbonate, potassium carbonate, potassium hydroxide, or mixtures thereof.

53. A method comprising:

producing mostly β,δ-epoxides of steroids by epoxidation reactions of δ-unsaturated 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), OCH₃, OCH₂, OCOOR (where R=alkyl or aryl), OSiRₓ'₆Rₓ₅Rₓ₃ (where Rₓ', Rₓ₅' or Rₓ₃'=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), OCH₃, OCH₂, OCOOR (where R=alkyl or aryl), OSiRₓ'₆Rₓ₅Rₓ₃ (where Rₓ', Rₓ₅' or Rₓ₃'=alkyl or aryl), halogen, CN, NO₂, alkyl, and aryl; or,

X₃ and X₄ in formula (XIII) are selected from the group consisting of O, OCH₃, and OCH₂CH₂O;

R₈ in formula (XIII) is selected from H, OR (where R=H or alkyl), OCH₃, OCH₂, OCOOR (where R=alkyl or aryl), OSiRₓ'₆Rₓ₅Rₓ₃ (where Rₓ', Rₓ₅' or Rₓ₃'=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), OCH₃, OCH₂, OCOOR (where R=alkyl or aryl), OSiRₓ'₆Rₓ₅Rₓ₃ (where Rₓ', Rₓ₅' or Rₓ₃'=alkyl or aryl), halogen, CN, alkyl, aryl, and COOR (where R=H, alkyl or aryl), and COCH₂OCOR (where R=alkyl or aryl), COCH₂F, COOR (where R=H or alkyl), O(CH₂CH₂O)OR (where R=alkyl), O(CH₂CH₂O)CH₂OR (where R=H or alkyl), O(CH₂CH₂O)CH₂OCOR (where R=alkyl or aryl), and O(CH₂CH₂O)CH₂F; or R₈ and R₁₀ in formula (XIII) are selected from the group consisting of O, OCH₃, and OCH₂CH₂O;
$R_{12}$ 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''$_3$ (where R', R'' or R'=alkyl or aryl);

$R_{14}$ and $R_{15}$ 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);

$R_{16}$ or $R_{17}$ in formula (XIV) is selected from alkyl and aryl;

$R_{18}$ or $R_{19}$ in formula (XIV) 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);

$R_{20}$ or $R_{21}$ 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, SO$_2$, and NR (where R=H or alkyl);

$R_{22}$ or $R_{23}$ 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);

$R_{24}$ or $R_{25}$ in formula (XV) is selected from H, halogen, C$_1$-C$_4$ alkyl, halogenated alkyl, and OCOR (where R=alkyl or aryl);

$R_{26}$ or $R_{27}$ 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, OTf$_2$, OTe, OCOR (where R=alkyl or aryl), and OSiR'$_3$R''$_3$ (where R', R'' or R'=alkyl or aryl).

$R_{28}$ or $R_{29}$ in formula (XVI) is selected from C$_1$-C$_4$ alkyl, halogenated alkyl, CH$_2$OCOR (where R=alkyl or aryl); and

$R_{27}$ 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

$R_{29}$ or $R_{30}$ in formula (XVI) is selected from C$_1$-C$_4$ alkyl, halogenated alkyl, CH$_2$OCOR (where R=alkyl or aryl); and

$R_{31}$ or $R_{32}$ in formula (XVI) is selected from C$_1$-C$_4$ alkyl, halogenated alkyl, CH$_2$OCOR (where R=alkyl or aryl); and

$R_{33}$ or $R_{34}$ in formula (XVI) is selected from C$_1$-C$_4$ alkyl, halogenated alkyl, CH$_2$OCOR (where R=alkyl or aryl); and

$R_{35}$ or $R_{36}$ in formula (XVI) is selected from C$_1$-C$_4$ alkyl, halogenated alkyl, CH$_2$OCOR (where R=alkyl or aryl); and