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Oxidation of unsaturated steroid ketones with hydrogen peroxide catalyzed by Fe(bpmen)(OTf)$_2$. New methodology to access biologically active steroids by chemo-, and stereoselective processes

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ABSTRACT

In this paper we describe a new environmentally friendly method to promote the oxidation of steroids. The chemo- and stereoselective aspects of the oxidation of conjugated enones, dienones, further unsaturated enones, estrone, and cholestane acetates were under study.
The great facial stereoselectivity of the method has been shown on substrates **12**, **14**, and **18** improving some of the updated reported procedures in the literature. Reaction with substrate **16** displays the competition between the C4–C5 and the C9–C11 double bonds. The steric hindrance around C ring activates the C–H hydroxylation at the allylic position on C-12 by formation of the allylic alcohol **17c**. The C–H activation at C-5 was proven to succeed on the oxidation reaction of androstane **26** by formation of the tertiary alcohol **27**.

1. Introduction

Nature's capacity to catalyze the oxidation of unactivated C–H bonds, the epoxidation and dihydroxylation of carbon–carbon double bonds in steroids employing enzymatic systems has been known for a long time.[1] However, attempts to mimic natural methods by replacing a hydrogen atom bonded to an unactivated carbon of a steroid with a hydroxyl group while maintaining the integrity of the carbon atom, and by regio- and stereoselective epoxidation and dihydroxylation of unsaturated steroids, constitute a huge challenge. In nature, most of the significant enzymatic transformations involve oxidation by metalloporphyrins through catalytic processes.[2] In the aim to propose an artificial cytochrome P450 enzyme, the use of attached templates to promote remote functionalization of steroids was introduced by Breslow in 1980,[3] the direct transformation of steroids with high predictability and specificity has yet to be accomplished and constitutes an area of increasing interest.

Recently, Pellissier and Santelli have summarized the most outstanding contributions to the chemical and biochemical hydroxylation of steroids.[4] Among others, they pointed directly to hydroxylations achieved by oxidants like iodosobenzene,[5] *N*-tosyliminophenyliodinane,[6] 2,6-dichloropyridine *N*-oxide,[7] and cumene hydroperoxide,[8] in oxidative processes catalyzed by metal porphyrins, where manganese Mn(III), ruthenium Ru(II), and iron Fe (III), play relevant activating roles.

Furthermore, Salvador and col. have reviewed the contributions on catalytic epoxidation, *syn*-dihydroxylation, allylic oxidation, alcohol oxidation, and remote functionalization reactions in steroid chemistry.[9] However, even when focus has been given to catalytic processes, most of the transformations promoted by metal complexes are porphyrin-type derivatives of Ru (II),[10] Ru (IV),[11] Ru(VI),[12] Mn(III),[13,16] Fe(III).[14] Special attention has been paid to catalytic remote functionalization promoted by Fe(III),[8] Mn(III),[5,6,13,15] and Ru(II),[10a] porphyrin derivatives.

Cavaleiro and col. reported in 2004 on the oxidation reactions of Δ^4- and Δ^5-steroids with hydrogen peroxide catalyzed by porphyrin complexes of Mn(II) and Fe(III).[16] These metalloporphyrins efficiently catalyze the epoxidation reactions of 17β-acetoxy-4-androstene 1,4-cholestene **2**, and 3β-acetoxy-5-cholestene **3** in the presence of H_2O_2 as oxygen donor (Scheme 1). Porphyrins with bulky, electron-withdrawing groups in the *ortho* positions of the *meso* phenyls and with Mn^{III} as the central metal ion, such as [Mn(tdcpp)Cl], gave preferentially the β-epoxide of Δ^4- and Δ^5-steroids (**4b**, **5b**, and **6b**). However, [Fe(tpfpp)Cl] catalyzes preferentially the α-epoxidation of Δ^4-steroids (**4a** and **5a**), and increases the α-stereoselectivity in the epoxidation of Δ^5-steroids (**6a**). Based

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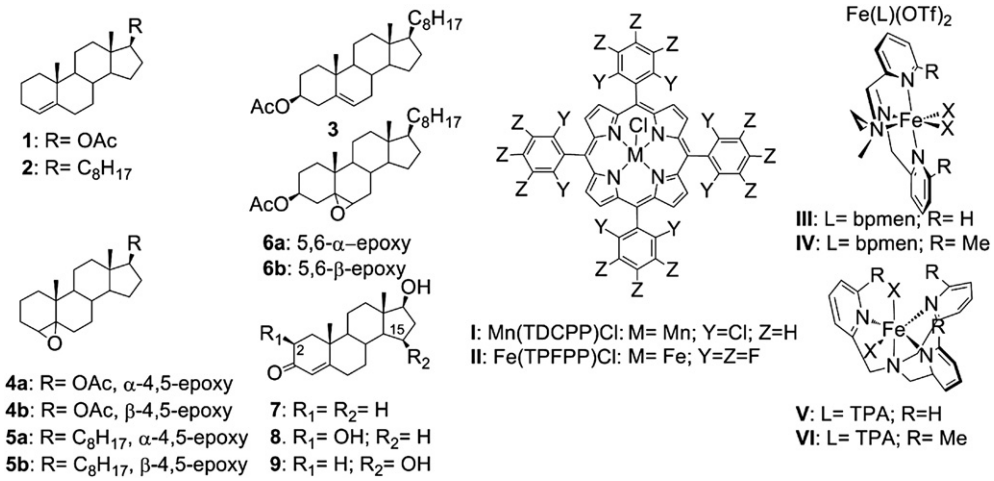


Scheme 1.

on the experimental data, the authors make a mechanistic proposal involving an oxo species for the β-approach and a peroxy species for the α-approach.[17]

In 2011 Reetz and col. reported their results on the regio- and stereoselectivity of the P450-catalyzed hydroxylation of steroids based on directed evolution of Cytochrome P450 enzymes. Using P450 BM3(F87A) as the starting enzyme and testosterone (**7**) as the substrate, they obtained a 1:1 mixture of the 2β- and 15β-alcohols (**8** and **9**, respectively). However, they obtained mutants of the enzyme that were 96–97% selective for either of the two regioisomers.[18]

During the last two decades great efforts have been devoted to the preparation of bio-inspired non-heme iron complexes capable of not only oxidizing hydrocarbons to alcohols, but also epoxidation and *cis*-dihydroxylation of olefins by using H_2O_2. Among them, the Fe(II) complexes, Fe(bpmen)$(OTf)_2$ (**III**), Fe(6-Me_2-bpmen)$(OTf)_2$ (**IV**) [bpmen: *N*,*N*′-dimethyl-*N*,*N*′-bis(2pyridylmethyl)-1,2-diaminoethane], [Fe(tpa) $(CH_3CN)_2](OTf)_2$ (**V**), and [Fe(6-Me_3-tpa)$(CH_3CN)_2](OTf)_2$ (**VI**), [tpa=tris(2-pyridylmethyl)amine], were reported to allow stereospecific alkane hydroxylation,[19] epoxidation,[20] and dihydroxylation of C=C double bonds.[21]

2. Results and discussion

The chemical modification of the steroid backbone can lead to significant biological effects.[22] Compounds like exemestane (6-methyleneandrosta-1,4-diene-3,17-dione),[23] and formestane (4-hydroxyandrostene-3,17-dione),[24] have been found to be effective as aromatase inhibitors by blocking the estrogen biosynthesis and thereby used as anti-breast cancer medication for postmenopausal women.[25] Furthermore, the capacity of progesterone and nestorone (16-methylene-17α-acetoxy-19-norpregn-4-ene-3,20-dione) for myelin repair, a major therapeutic challenge in demyelinating diseases, such as multiple sclerosis, has been recently discovered.[26] Stereoselective strategies for the modification of the steroid backbone aimed to improve the activity of these compounds are challenging goals.[27]

To the best of our knowledge no report has been given on the catalytic oxidation of steroids by using non-heme iron complexes of type **III** in the presence of H_2O_2 as oxygen donor. In this paper we describe a new environmentally friendly method to promote the oxidation of steroids. The chemo- and stereoselective aspects of the oxidation of conjugated enones, dienones, further unsaturated enones, estrone derivatives, and cholestane acetate were under study.

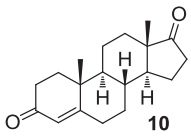
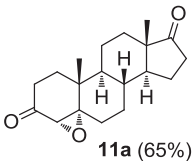
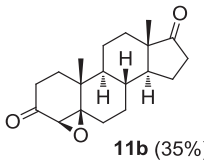
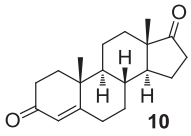
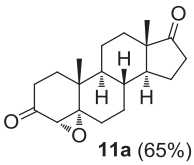
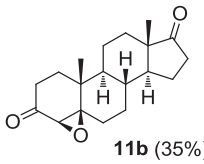
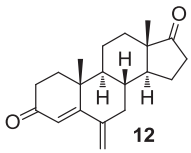
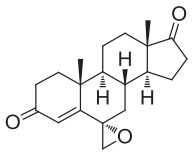
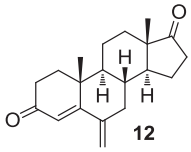
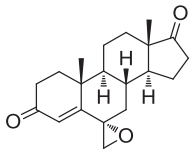
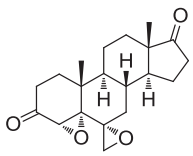
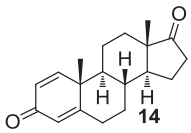
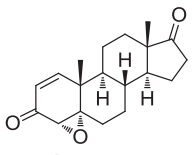
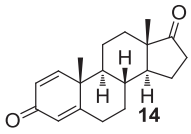
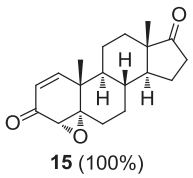
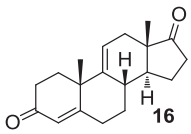
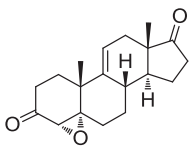
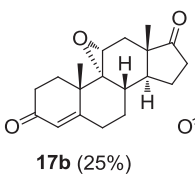
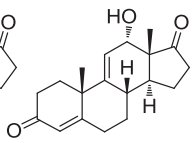
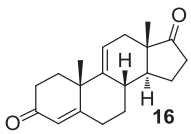
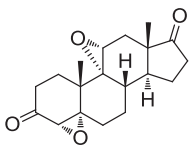
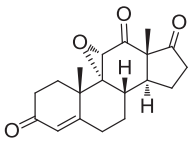
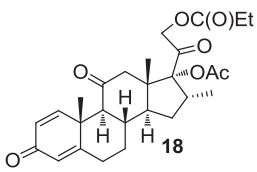
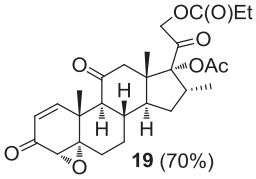
The acetates **20**, **22**, and **24** were obtained from the precursor alcohols by treatment with acetic anhydride under perchloric acid catalysis in the case of **20**, or under pyridine catalysis in the case of **24**. The isolation of acetate **22** was possible by treatment of estrone with isopropenyl acetate in the presence of iodine at 90 °C.[28] The oxidation reactions were carried out at room temperature with progressive addition of H_2O_2, in the open air (see Experimental part). The reactions were followed by TLC and were stopped after 10 min (method A), and after 30 min (method B). The product mixtures resulting from substrates oxidation reactions were fractionated by column chromatography and identified by comparing their ^1H NMR and ^{13}C NMR spectra with literature data. Table 1 summarizes our results.

The catalytic oxidation of 4-androsten-3,17-dione (**10**) with hydrogen peroxide in the presence of Fe(bpmen)$(OTf)_2$ afforded the same mixture of epoxides **11a**/**11b**=65:35 independently of the catalyst charge (method A: 5%; method B: 15%) (Table 1, entries 1 and 2). However, only in the second case (method B) the reaction went to completion after 30 min. The oxidative process under method A occurred with only 70% conversion. This oxidative transformation allowed us to isolate the two epoxides by flash chromatography and unambiguously assign the structure of both products. According to the literature, the ^{13}C NMR chemical shift corresponding to the C-19 in 4,5-epoxiandrostanes appear upfield in α epoxides (δ=17.4 ppm) compared to β-epoxides (δ=19.2 ppm);[16] However, the ^1H NMR chemical shift of the H-4 proton appears downfield (δ=2.93 ppm) in α-epoxides compared to β-epoxides (δ=2.90 ppm); therefore, the structural assignments found for **11a** (δ=16.6 ppm and δ=3.00 ppm) and **11b** (δ=19.1 ppm and δ=2.94) are shown in Table 1 as indicated.

We were interested to study the regioselectivity of the epoxidation reaction in androstanes with two double bonds [cross-conjugated (**14**, **18**), linear-conjugated (**12**), and not-conjugated (**16**, **20**)] with the carbonyl group. With the double-conjugated dienones 1,4-androstadien-3,17-dione **14**, and 17α-acetoxy-21-hydroxy-16α-methyl-3,11,20-trioxo-1,4-dien-21-propionate **18**, the oxidation reactions proceeded stereoselective to the 4,5-α-epoxides **15** and **19**, with 100% and 70% yields, respectively (Table 1, entries 5 and 9). In the first case with 60% conversion independently of the catalyst charge (methods A & B), and in the second case, with 50% conversion for a 15% catalyst charge.

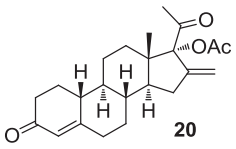
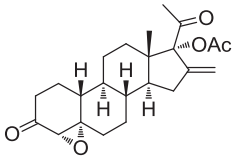
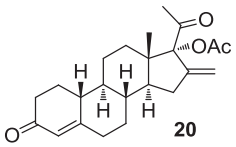
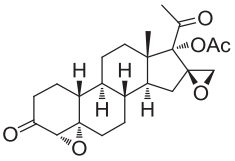
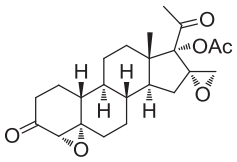
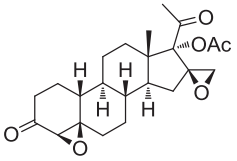
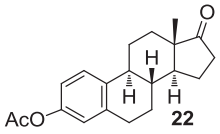
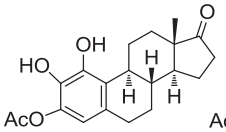
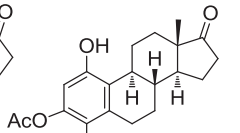
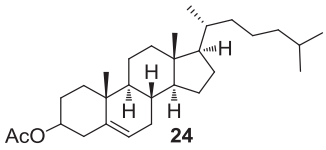
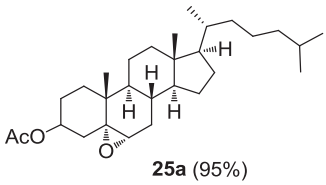
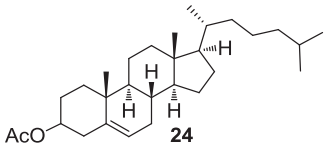
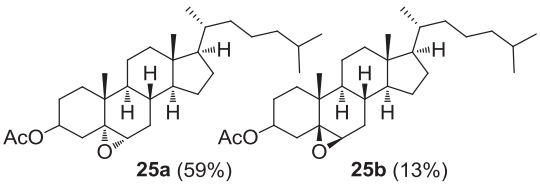
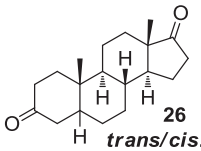
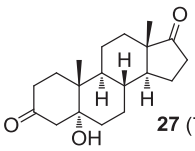
The structural assignments of epoxides **15** and **19** have been made based on the proton and carbon displacements found for H-4

Table 1
Oxidation of unsaturated steroids with hydrogen peroxide in the presence of $Fe(bpmen)(OTf)_2$

Entry	Substrate	Protocol[a]	Conversion (%)	Oxidation products (% yield)[b]
1	 **10**	A	70	 **11a** (65%)  **11b** (35%)
2	 **10**	B	100	 **11a** (65%)  **11b** (35%)
3	 **12**	A	100	 **13a** (100%)
4	 **12**	B	100	 **13a** (50%)  **13b** (30%)
5	 **14**	A	60	 **15** (100%)
6	 **14**	B	60	 **15** (100%)
7	 **16**	A	40	 **17a** (25%)  **17b** (25%)  **17c** (25%)
8	 **16**	B	100	 **17d** (50%)  **17e** (25%) **17a + 17b** (10%)
9	 **18**	B	50	 **19** (70%)

(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate	Protocol[a]	Conversion (%)	Products (%yield)[b]
10	 **20**	A	15	 **21a** (100%)
11	 **20**	B	30	 **21b** (36%)  **21c** (28 %)  **21d** (36%)
12	 **22**	B	16	 **23a**(63%)  **23b** (37%)
13	 **24**	A	90	 **25a** (95%)
14	 **24**	B	100	 **25a** (59%) **25b** (13%) +Σ **lateral chain oxdn products** (28%)
15	 **26** ***trans/cis: 8/2***	B	30	 **27** (70%)

[a] Protocol A: 5% mol of catalyst, 1 equiv of H_2O_2, 0.5 equiv of AcOH, reaction time:10 min. Protocol B: 15% mol of catalyst, 3 equiv of H_2O_2, 1.5 equiv of AcOH, reaction time: 30 min.

[b] Yields were calculated based on recovered starting material.

and C-19 in the ^{1}H NMR and ^{13}C NMR spectra for both products according to the literature data.[16]

The oxidation of 6-methylen-4-androsten-3,17-dione **12** with H_2O_2 in the presence of Fe(bpmen)$(OTf)_2$, provided the external epoxide **13a** with quantitative yields by applying method A (Table 1, entry 3); however, increasing the catalyst charge (method B) provided the mixture of the monoepoxide **13a** (50%) and the diepoxide **13b** (30%) (Table 1, entry 4). Again, the proton and carbon

displacements found for H-4 and C-19 in the ^{1}H NMR and ^{13}C NMR spectra for both products resulted to be crucial for structural assignments based on literature precedents of similar transformations.[23] The first result (method A) may be highlighted as a regio- and stereoselective transformation since it is known that the *m*-CPBA (*m*-chloroperbenzoic acid) oxidation of exemestane led to an epimeric mixture of 6α- and 6β-spirooxiranandrosta-1,4-diene-3,17-diones.[23b]

The 4,9(11)-androstadien-3,17-dione **16** afforded complex mixtures following both procedures A and B (Table 1, entries 7 and 8). With 5% of catalyst charge the reaction proceeded with a modest conversion (40%) and afforded an equimolecular mixture of the monoepoxides **17a** (25%), **17b** (25%) and the product of the allylic hydroxylation **17c** (25%). The assignment of the resonances in the ^{1}H and ^{13}C NMR spectra of compounds **17a**, **17b**, and **17c** was achieved by using dimensional techniques, namely COSY ($^{1}H/^{1}H$), HMQC ($^{1}H/^{13}C$) and HMBC ($^{1}H/^{13}C$-long range) experiments, as well as by DEPT techniques (see Supplementary data). With 15% of catalyst charge, the oxidative transformation went to completion and afforded a complex reaction mixture in which, the diepoxide **17d** was the major product (50%); in addition, the epoxy ketone **17e** (25%) and a mixture of the monoepoxides **17a** and **17b** (10%) were also isolated. We assume by mechanistic reasons that the formation of **17e** should be preceeded by the formation of **17c** through a three-step sequence: allylic C–H activation of **16**, alcohol oxidation to the enone, and epoxidation of the enone.

By applying method A (Table 1, entry 10), the oxidation of nestorone **20** led to the monoepoxide **21a** with quantitative yields but low conversions (15%). However, by increasing the catalyst charge (method B, entry 11) the oxidation led to a mixture of diepoxides **21b** (36%), **21c** (28%), and **21d** (36%) with double degree of conversion (30%). Again, the structural assignments were based on spectral data of related oxidation products.[16]

The oxidation of 3β-acetoxy-5-cholestene afforded the α-epoxide **25a** with 95% yield and 90% conversion by applying method A (Table 1 entry 13). Increasing the catalyst charge to 15% (method B, entry 14) the oxidation reaction afforded the mixture of epoxides **25a** (59%) and **25b** (13%) together with an irresolvable mixture of epoxides, which also showed oxidation at the lateral chain (28%). The structural assignments were possible by comparison with the spectral data given for **25a** and **25b** in the literature.[16]

The oxidation of estrone acetate **22** by method B (Table 1, entry 12) afforded the mixture of 1,2-dihydroxy acetate **23a** (63%) and 1,4-dihydroxy acetate **23b** (37%) with low conversions (16%).

The iron-promoted C–H activation on saturated androstane derivatives would open new approaches to interesting starting materials. Aimed to this target we decided to try the C–H activation on saturated androstanes. The oxidation reaction of 3,17-androstanedione **26** (trans/cis=80:20), by method A led to the 5-hydroxy derivative **27** with 67% yield and 30% of conversion. This derivative corresponds to the C–H activation product at the C-5 center in the androstane backbone. The assignment of the configuration α at C-5 of **27** was possible by comparison of the spectral data obtained for **27** [^{13}C NMR δ: 13.10 (C-18), 15.4 (C-19), and 77.7 (C-5)] and the ones described in the literature for 5β-hydroxyandrostane-3,17-dione[29] [^{13}C NMR δ: 13.8 (C-18), 16.2 (C-19), and 78.4 (C-5)] and for 5α-hydroxyandrostane-3,17-dione[30] [^{13}C NMR δ: 13.8 (C-18), 15.7 (C-19), and 77.4 (C-5)]. Treatment of **27** with chlorosulfonic acid in dichloromethane at 0 °C led to **10** in quantitative yields.

3. Conclusions

In this paper a new environmentally friendly methodology for oxidation of biologically active steroids is under study. The oxidation of different steroid enones with hydrogen peroxide is catalyzed by Fe(bpmen)$(OTf)_2$. The mild open-air conditions, short reaction times and, in some cases the high yields obtained, are promising enough to apply this method to other types of compounds.

The Fe(bpmen)$(OTf)_2$ complex has been shown like an efficient catalyst in the presence of H_2O_2 for epoxidation reactions. The great facial stereoselectivity has been shown on substrates like **12**, **14**, and **18** improving some of the updated reported procedures in the literature. Furthermore, it is worth to mention the chemoselectivity developed by the catalyst against certain dienic systems like **14** and **18**, where only the more electronic-rich double bond reacts with the oxidant.

Other issue, which is been discussed in the paper is the possibility of activating C–H bonds by the same complex Fe(bpmen)$(OTf)_2$. The reaction with substrate **16** displays the competition between the C4–C5 and the C9–C11 double bonds. In this case, the great steric hindrance for the complex to approach C-ring of the steroid is driving the activation to the allylic position C-12; therefore, making the C–H activation to compete with the epoxidation reaction.

Having into account the competition between epoxidation and C–H activation, clearly driven to the epoxidation with this complex, we tried this methodology on substrate **26**, an androstane diketone lacking of all types of C–C unsaturation. This reaction showed the great synthetic C–H activation potential of complex Fe(bpmen)$(OTf)_2$ by giving rise to the exclusive formation of the 5α-hydroxy derivative **27**.

4. Experimental section

4.1. General experimental methods

^{1}H NMR spectra were measured at either 200 or 400 MHz and ^{13}C NMR were measured at 50 or 100 MHz in $CDCl_3$ and referenced to TMS (^{1}H) or solvent (^{13}C), except where indicated otherwise. HRMS determinations were recorded at the Mass Spectrometry Service of the University of Salamanca, Spain, in an Applied Biosystems QSTAR XL with ESI ionization. HPLC–MS analysis of **11a** and **11b** was performed using a Waters XBridge C18, 3.5 μm, 2.1×100 mm column. Chemicals and solvents were obtained from commercial sources and used as received with the exception of tetrahydrofuran, which was distilled from sodium and benzophenone. Yields reported are for chromatographic pure isolated products unless mentioned otherwise. Preparation of the catalyst Fe(bpmen)$(OTf)_2$ (**III**) was achieved according to the literature.[19g]

4.2. Method A (5 mol % of catalyst)

A 10 mL round bottom flask was charged with: 0.75 mL of a 0.33 M AcOH solution in CH_3CN, Fe(bpmen)$(OTf)_2$ (15.6 mg, 0.025 mmol, 5 mol %), and substrate (0.5 mmol, 1.0 equiv). The solution was stirred vigorously at room temperature. A solution of H_2O_2 (30 wt %, 68 μL, 0.6 mmol, 1.2 equiv) in CH_3CN (4 mL, 0.13 M) was added dropwise via syringe. After addition was completed, the reaction mixture was stirred for additional 10 min. Then $NaHCO_3$ saturated aqueous solution was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, evaporated under reduced pressure, and purified by flash chromatography.

4.3. Method B (15 mol % of catalyst)

A 50 mL round bottom flask was charged with: 0.75 mL of a 0.33 M AcOH solution in CH_3CN, Fe(bpmen)$(OTf)_2$ (15.6 mg, 0.025 mmol, 5 mol %), and substrate (0.5 mmol, 1.0 equiv). The solution was stirred vigorously at room temperature. A solution of H_2O_2 (30 wt %, 68 μL, 0.6 mmol, 1.2 equiv) in CH_3CN (4 mL, 0.13 M)

was added dropwise via syringe. After stirring for 10 min, 0.5 mL of a 0.5 M AcOH solution in CH_3CN and Fe(bpmen)$(OTf)_2$ (15.6 mg, 0.025 mmol, 5 mol %) were added. This was followed by the dropwise addition of H_2O_2 (30 wt %, 68 μL, 0.6 mmol, 1.2 equiv) in CH_3CN (4 mL, 0.13 M). A third addition was performed for a total of 15 mol % Fe(bpmen)$(OTf)_2$, 1.5 equiv of AcOH, and 3.6 equiv of H_2O_2. After the last 10 min of stirring $NaHCO_3$ saturated aqueous solution was added and the mixture was extracted with ethyl acetate. The combined organic layers were dried over anhydrous Na_2SO_4, evaporated under reduced pressure, and purified by flash chromatography.

4.4. 4,5α-Epoxy-androstan-3,17-dione and 4,5β-epoxy-androstan-3,17-dione 11a and 11b

Compound **11a**: Retention time: 12.56 min. ^{1}H NMR ($CDCl_3$): δ=3.00 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=13.9 (q), 16.6 (q), 20.8 (t), 21.9 (t), 27.9 (t), 29.2 (t), 29.6 (t), 33.2 (t), 31.5 (t), 35.1 (d), 35.9 (t), 37.0 (s), 51.0 (d), 47.9 (s), 51.0 (d), 63.0 (d), 70.1 (s), 206.8 (s), 220.7 (s) ppm. ESIMS: *m*/*z* 303.2 [M^+]. *Compound* **11b**: Retention time: 12.88 min. ^{1}H NMR (17$CDCl_3$): δ=2.94 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=13.9 (q), 19.1 (q), 21.0 (t), 21.9 (t), 26.3 (t), 29.3 (t), 29.7 (t), 31.2 (t), 32.6 (t), 34.8 (d), 35.9 (t), 37.5 (s), 46.8 (d), 47.8 (s), 50.8 (d), 62.7 (d), 70.0 (s), 206.5 (s), 220.0 (s) ppm. ESIMS: *m*/*z* 303.2 [M^+].

4.5. 6α-Spiroxirandrost-4-ene-3,17-dione 13a

^{1}H NMR ($CDCl_3$): δ=0.90 (s, 3H), 1.20 (s, 3H), 2.52 (d, *J*=6 Hz, 1H), 2.87 (d, *J*=6 Hz, 1H), 5.97 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=13.9 (q), 17.9 (q), 20.3 (t), 21.9 (t), 31.3 (t), 34.0 (t), 34.2 (d), 35.8 (t), 36.0 (t), 37.8 (t), 39.8 (s), 47.7 (s), 51.0 (d), 52.8 (d), 56.9 (s), 58.7 (s), 119.9 (d), 167.2 (s), 199.0 (s), 219.9 (s) ppm. ESI−HRMS ($M-H^+$): calculated for $C_{20}H_{27}O_3$: 315.1954, experimental: 315.1956.

4.6. 4,5α-Epoxy-6α-spiroxirandrostan-3,17-dione 13b

^{1}H NMR ($CDCl_3$): δ=0.91 (s, 3H), 1.09 (s, 3H), 2.65 (d, *J*=4.8 Hz, 1H), 2.82 (d, *J*=4.8 Hz, 1H), 3.26 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=13.9 (q), 16.0 (q), 20.7 (t), 21.9 (t), 29.1 (t), 31.3 (t), 33.0 (t), 34.7 (d), 35.5 (t), 35.8 (t), 38.7 (s), 47.8 (s), 50.3 (d), 50.8 (d), 54.1 (s), 54.6 (t), 57.2 (d), 71.5 (s), 205.8 (s), 219.9 (s) ppm. ESI−HRMS (M^++Na): calculated for $C_{20}H_{26}O_4Na$: 353.1723, experimental: 353.1721.

4.7. 4,5-Epoxy-androst-1-ene-3,17-dione 15

^{1}H NMR ($CDCl_3$): δ=0.90 (s, 3H), 1.32 (s, 3H), 3.21 (d, *J*=1.8 Hz, 1H), 5.87 (dd, J_1=1.8 Hz, J_2=10.6 Hz, 1H), 6.47 (d, *J*=10.6 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=13.9 (q), 16.4 (q), 21.7 (t), 21.9 (t), 28.9 (t), 30.0 (t), 31.2 (t), 34.9 (d), 35.7 (t), 42.5 (s), 47.6 (s), 50.5 (d), 54.2 (d), 62.5 (d), 67.1 (s), 123.6 (d), 155.1 (d), 195.8 (s), 220.0 (s) ppm. ESI−HRMS (M^++Na): calculated for $C_{19}H_{24}O_3Na$: 323.1617, experimental: 323.1608.

4.8. 12α-Hydroxy-androst-4,9(11)-diene-3,17-dione 17c

^{1}H NMR ($CDCl_3$): δ=0.83 (s, 3H), 1.25 (s, 3H), 4.19 (d, *J*=5.6 Hz, 1H), 5.69 (dd, J_1=1.8 Hz, J_2=5.6 Hz, 1H), 5.77 (d, *J*=1.8 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=12.7 (q), 21.9 (t), 26.5 (q), 30.2 (t), 32.3 (t), 33.5 (t), 34.0 (t), 36.8 (t), 37.1 (d), 41.1 (d), 51.6 (s), 68.9 (d), 119.0 (d), 124.6 (d), 151.0 (s), 167.8 (s), 179.7 (s), 198.6 (s), 220.3 (s) ppm. ESI−HRMS (M^++Na): calculated for $C_{19}H_{24}O_3Na$: 323.1601, experimental: 323.1609.

4.9. 4,5α-9α,11-Diepoxy-androstan-3,17-dione 17d

^{1}H NMR ($CDCl_3$): δ=0.90 (s, 3H), 1.31 (s, 3H), 1.85 (d, *J*=3.0 Hz, 2H), 3.02 (s, 1H), 3.15 (dd, J_1=3.0 Hz, J_2=3.0 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=16.6 (q), 19.9 (q), 22.1 (t), 22.2 (t), 25.1 (t), 30.2 (t), 31.7 (t), 32.5 (t), 35.1 (d), 36.5 (t), 38.4 (s), 41.3 (d), 45.5 (s), 52.7 (d), 61.2 (d), 66.8 (s), 68.6 (s), 206.3 (s), 220.6 (s) ppm. ESI−HRMS (M^++Na): calculated for $C_{19}H_{24}O_4Na$: 339.1566, experimental: 339.1561.

4.10. 9a,11-Epoxy-androst-4-ene-3,12,17-trione 17e

^{1}H NMR ($CDCl_3$): δ=1.13 (s, 3H), 1.33 (s, 3H), 3.15 (s, 1H), 5.86 (d, *J*=2.2 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=14.5 (q), 21.2 (t), 24.3 (q), 27.0 (t), 27.9 (t), 28.9 (t), 32.9 (t), 37.0 (t), 37.3 (d), 40.5 (s), 47.9 (d), 53.7 (s), 62.6 (d), 68.9 (s), 123.6 (d), 167.2 (s), 196.3 (s), 204.9 (s), 211.3 (s) ppm. ESI−HRMS (M^++Na): calculated for $C_{19}H_{22}O_4Na$: 337.1410, experimental: 337.1402.

4.11. 17α-Acetoxy-4,5α-epoxy-21-hydroxy-16α-methyl-3,11,20-trioxo-1-pregnene propionate 19

^{1}H NMR ($CDCl_3$): δ=0.76 (s, 3H), 0.96 (d, *J*=4.8 Hz, 3H), 1.14 (t, J_1=7.6 Hz, J_2=6 Hz, 3H), 1.45 (s, 3H), 2.11 (s, 3H), 3.17 (d, *J*=2 Hz, 1H), 4.72 (ddd, J_1=16 Hz, J_2=11.6 Hz, J_3=2 Hz, 2H), 5.79 (dd, J_1=10.6 Hz, J_2=2 Hz, 1H), 7.08 (d, *J*=10.6 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=9.2 (q), 15.5 (q), 16.2 (q), 17.3 (q), 20.6 (q), 27.3 (t), 29.7 (t), 30.5 (t), 33.3 (t), 35.8 (d), 36.2 (d), 41.4 (s), 48.1 (d), 49.6 (t), 51.7 (s), 62.3 (d), 64.3 (d), 66.2 (s), 67.0 (t), 94.0 (s), 123.1 (d), 155.0 (d), 170.7 (s), 174.0 (s), 195.9 (s), 197.8 (s), 207.3 (s) ppm. ESI−HRMS (M^++Na): calculated for $C_{27}H_{34}O_8Na$: 509.2145, experimental: 509.2150.

4.12. 17α-Hydroxy-4,5α-epoxy-16-methylene-3,20-dioxo-pregnane acetate 21a

^{1}H NMR ($CDCl_3$): δ=0.72 (s, 3H), 2.13 (s, 3H), 2.14 (s, 3H), 3.06 (s, 1H), 5.43 (s, 1H), 5.57 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=14.6 (q), 17.0 (t), 21.5 (q), 26.0 (t), 27.8 (q), 30.3 (t), 30.6 (t), 31.9 (t), 32.8 (t), 33.4 (t), 40.2 (d), 40.7 (d), 43.5 (d), 47.3 (d), 47.9 (s), 62.0 (d), 67.7 (s), 94.2 (t), 144.7 (s), 170.4 (s), 202.8 (s), 207.0 (s) ppm. ESIMS: *m*/*z* 387.3 [M+H], 409.3 [M+Na].

4.13. 17α-Hydroxy-4,5α-epoxy-3,20-dioxo-16β-spiroxiran-pregnane acetate 21b

^{1}H NMR ($CDCl_3$): δ=1.06 (s, 3H), 2.07 (s, 3H), 2.28 (s, 3H), 3.06 (s, 1H), 3.06 (dd, J_1=5.6 Hz, J_2=107 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ=14.5 (q), 16.9 (d), 21.2 (q), 25.6 (d), 29.9 (d), 30.0 (d), 30.3 (d), 31.6 (q), 31.9 (d), 33.4 (d), 34.4 (d), 40.1 (t), 40.8 (t), 43.7 (t), 45.7 (t), 49.6 (s), 50.8 (d), 62.0 (t), 64.7 (s), 67.6 (s), 91.8 (s), 170.5 (s), 202.7 (s), 207.0 (s) ppm. ESIMS: *m*/*z* 403.3 [M+H], 425.3 [M+Na].

4.14. 17α-Hydroxy-4,5α-epoxy-3,20-dioxo-16α-spiroxiran-pregnane acetate 21c

^{1}H NMR ($CDCl_3$): δ=1.06 (s, 3H), 1.42 (s, 3H), 1.72 (s, 3H), 3.03 (s, 1H), 4.05 (dd, J_1=10.2 Hz, J_2=42 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ=14.8 (q), 17.1 (t), 23.0 (q), 26.0 (t), 29.9 (t), 30.3 (t), 32.3 (q), 33.1 (t), 33.5 (t), 33.5 (t), 36.1 (d), 40.5 (d), 40.8 (s), 42.8 (d), 43.2 (d), 48.4 (t), 61.3 (s), 62.1 (d), 65.8 (s), 94.0 (s), 170.0 (s), 202.8 (s), 207.1 (s) ppm. ESIMS: *m*/*z* 403.3 [M+H], 425.3 [M+Na].

4.15. 17β-Hydroxy-4,5β-epoxy-3,20-dioxo-16β-spiroxiran-pregnane acetate 21d

^{1}H NMR ($CDCl_3$): δ=0.80 (s, 3H), 1.97 (s, 3H), 2.16 (s, 3H), 3.02 (s, 1H), 3.04 (dd, J_1=5 Hz, J_2=52 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ=15.1

(q), 20.6 (t), 20.8 (t), 26.0 (t), 27.4 (q), 28.6 (t), 29.9 (t), 33.1 (t), 35.7 (t), 36.5 (t), 39.9 (d), 40.6 (d), 45.6 (d), 47.4 (s), 48.3 (d), 54.1 (t), 61.8 (d), 64.6 (s), 65.1 (s), 93.5 (s), 171.4 (s), 202.5 (s), 205.8 (s) ppm. ESIMS: *m*/*z* 403.3 [M+H], 425.3 [M+Na].

4.16. 1,2,3-Trihydroxy-estra-17-oxo-1,3,5(10)-triene-3-acetate 23a

^{1}H NMR ($CDCl_3$): δ=0.92 (s, 3H), 2.33 (s, 3H), 6.43 (s, 1H) ppm. ESI–HRMS [M+Na]: calculated for $C_{20}H_{24}NaO_5$: 367.1521, experimental: 367.1509.

4.17. 1,3,4-Trihydroxy-estra-17-oxo-1,3,5(10)-triene-3-acetate 23b

^{1}H NMR ($CDCl_3$): δ=0.93 (s, 3H), 2.28 (s, 3H), 6.04 (d, *J*=1.8 Hz, 1H) ppm. ESI–HRMS [M+Na]: calculated for $C_{20}H_{24}NaO_5$: 367.1521, experimental: 367.1519.

4.18. 3-Hydroxy-5α,6-epoxy-cholestane acetate 25a

^{1}H NMR ($CDCl_3$): δ=0.58 (s, 3H), 0.82 (s, 3H), 0.85 (s, 3H), 0.88 (s, 3H), 1.00 (s, 3H), 2.01 (s, 3H), 2.17 (t, *J*=6 Hz, 1H), 2.89 (d, *J*=4.4 Hz, 1H), 4.92 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=12.0 (q), 16.0 (q), 18.8 (q), 20.8 (t), 21.5 (q), 22.7 (t), 23.0 (t), 24.0 (t), 24.2 (t), 27.4 (t), 28.2 (d), 28.2 (t), 28.9 (t), 30.0 (d), 32.3 (t), 35.0 (s), 35.9 (d), 36.3 (t), 36.3 (d), 39.5 (t), 42.5 (d), 42.6 (s), 56.0 (d), 56.9 (d), 59.3 (d), 65.3 (s), 71.6 (d), 170.4 (s) ppm. ESIMS: *m*/*z* 467.5 [M+Na].

4.19. 3-Hydroxy-5β,6-epoxy-cholestane acetate 25b

^{1}H NMR ($CDCl_3$): δ=0.63 (s, 3H), 0.80 (s, 3H), 0.84 (s, 3H), 0.87 (s, 3H), 0.91 (s, 3H), 2.00 (s, 3H), 2.75 (t, J_1=12 Hz, J_2=6 Hz, 1H), 2.91 (s, 1H), 5.00 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ=12.2 (q), 14.1 (q), 20.2 (t), 20.8 (q), 21.6 (q), 22.8 (q), 23.0 (q), 24.1 (t), 26.5 (t), 28.2 (d), 28.2 (d), 28.3 (t), 29.1 (t), 31.3 (t), 35.9 (d), 36.2 (t), 37.5 (t), 39.7 (t), 39.7 (t), 41.9 (t), 42.7 (s), 44.5 (s), 45.2 (d), 55.8 (d), 56.4 (d), 56.4 (d), 70.9 (d), 80.5 (s), 170.4 (s) ppm. ESIMS: *m*/*z* 367.5 [M−OAc], 385.5 [M−Ac], 467.5 [M+Na].

4.20. 5α-Hydroxy-androstan-3,17-dione 27

^{1}H NMR ($CDCl_3$): δ=0.87 (s, 3H), 1.01 (s, 3H), 2.98 (d, *J*=13 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$): δ=13.1 (q), 15.4 (q), 20.2 (t), 21.0 (t), 27.1 (t), 30.4 (t), 30.7 (t), 33.7 (d), 35.1 (t), 35.2 (t), 36.5 (t), 39.6 (s), 43.3 (d), 47.0 (s), 48.6 (t), 50.7 (d), 77.6 (s), 210.3 (s), 219.7 (s) ppm.

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Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.08.079.

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