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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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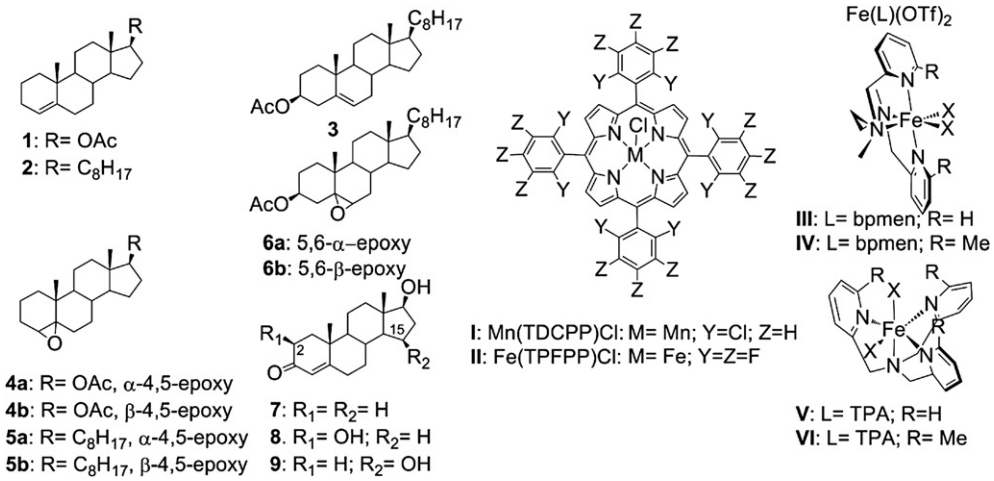

Scheme 1.

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