

STEREOSELECTIVE 7 α -HYDROXYLATION OF 3 β -ACETOXY- Δ^5 -STEROIDS BY Fe(PA)₃/H₂O₂/MeCN

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Stereoselective 7 α -hydroxylation reaction of Δ^5 -steroids by a Fe(PA; picolinate)₃/H₂O₂/MeCN system is presented. The 7 α -hydroxylation reactions were achieved in 33–40% yields by addition of 30%-H₂O₂ to a solution of 3 β -acetoxy- Δ^5 -steroids **1a–1d** and a crystalline of Fe(PA)₃ in MeCN.

KEY WORDS oxygenation; 7 α -hydroxylation; Fe(PA)₃/H₂O₂/MeCN; Δ^5 -steroid; Gif system

Stereoselective 7 α -hydroxylation of 3 β -acetoxy- Δ^5 -steroids is interesting in terms of the syntheses of recently discovered cytotoxic 3 β ,7 α -dihydroxy- Δ^5 -steroids¹⁾ and the metabolism of cholesterol by the cytochrome P-450 species 7 α -hydroxylase in the livers of most mammals. Many investigations on oxygenation reactions using simple, readily available reagent systems mimicking mono-oxygenase enzymes have been carried out. Of those, a study on iron(II) or iron(III) picolinate (PA) complexes as a catalyst of oxygenation reactions raised challenging problems. It was also noted that the oxidation reaction with H₂O₂ catalyzed by iron picolinate complexes varied depending on the solvents used.²⁾ Although many studies on iron picolinate complex /H₂O₂/solvent systems have been reported by the Sawyer group²⁾ and Barton group,³⁾ there has been no report to date on the oxidation reaction by the Fe^{III}(PA)₃/H₂O₂/MeCN system. We report that the modified system Fe(PA)₃/H₂O₂/MeCN as an alternative to the Gif system reagent is effective in stereoselective 7 α -hydroxylation of 3 β -acetoxy- Δ^5 steroids **1a–1d**.

The oxygenation reactions with this system of 3 β -acetoxy- Δ^5 -steroids, cholesterol acetate (**1a**), stigmasterol acetate (**1b**), pregnenolone acetate (**1c**), and dehydroisoandrosterone acetate (**1d**) were carried out according to the procedure shown in Table 1. The above reaction gave 7 α -hydroxy derivatives **2** (33–40% yields) along with a trace amount of 7 β -hydroxy derivatives **3**, 7-oxo derivatives **4** (16–23% yields), α and β epoxides mixtures **5** and **6** (3–13% yields), and recovered materials in all cases (Chart 1). The structural identification of **2** and **3** was done by comparing the physical data of the corresponding dihydroxy compounds prepared by hydrolysis with those of the respective authentic samples,^{4a,b,c)} respectively. The structure of **4**, **5**, and **6** was identified by comparison of the physical data with those of the respective authentic samples.^{4b,d,e)} In this investigation, we found that the most efficient and stereoselective 7 α -hydroxylation reaction was obtained in all cases using a molar ratio of substrate **1** : Fe(PA)₃ : 30% H₂O₂ = 1 : 0.5 : 3.

The reaction mechanism with substrates **1a–1d** using the present reagent system can be postulated as shown in Chart 2, and the complexes circulate in the order of (B)→(C)→(D)→(E) or (F)→→(B). Preferential 7-hydroxylation compared to 7-ketonization may be due to the greater formation of (E) relative to (F) as a result of the sufficient H₂O contained in 30% H₂O₂.

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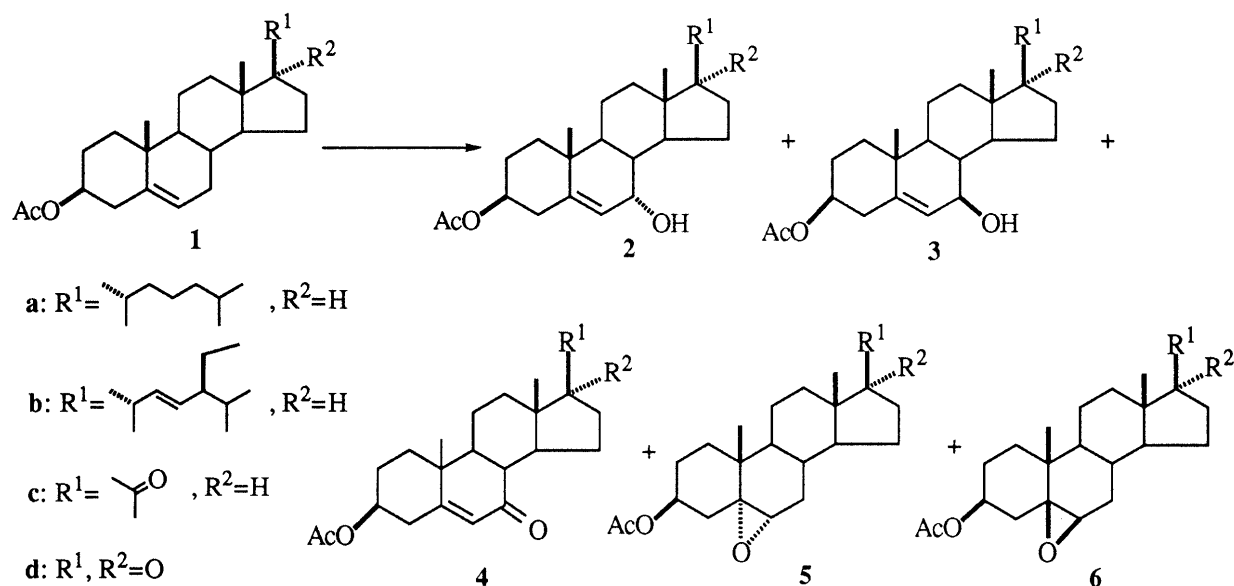
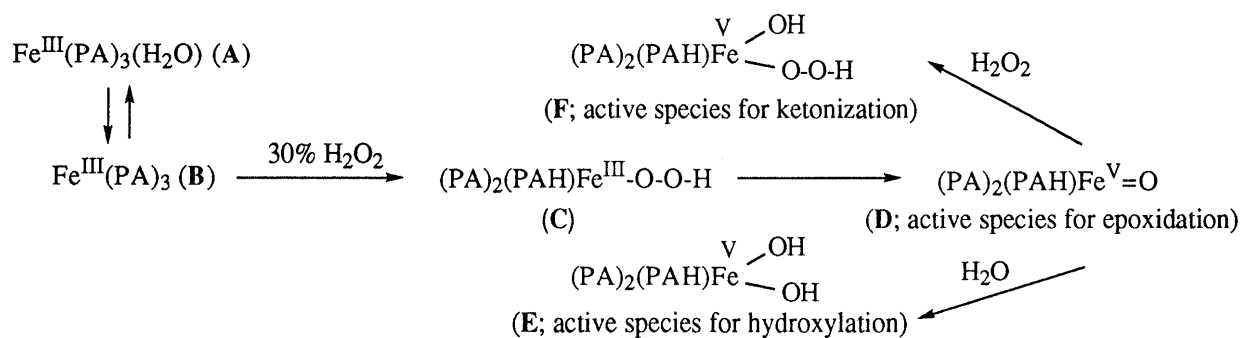


Chart 1

Table 1. Oxygenation of Δ^5 -Steroids **1a-1d** with $\text{Fe}(\text{PA})_3/\text{H}_2\text{O}_2/\text{MeCN}$ ^{a,b)}

Run	Substrate	Product (yield, %) ^{c)}					Recovery (%)	Mass balance (%)
		2 7 α -Hydroxy	3 7 β -Hydroxy	4 7-Oxo	5 α -Epoxy	6 β -Epoxy		
1	1a	2a (40.0)	3a (1.1)	4a (19.8)	5a (4.7)	6a (8.4)	22.6	96.6
2	1b	2b (36.5)	3b ^{d)}	4b (23.1)	5b (4.8)	6b (6.1)	24.7	95.2
3	1c	2c (33.1)	3c ^{d)}	4c (15.7)	5c (3.3)	6c (3.4)	19.9	75.4
4	1d	2d (39.3)	3d ^{d)}	4d (22.0)	5d (0.7)	6d (1.9)	19.8	83.7

^{a)} The iron complex $\text{Fe}(\text{PA})_3$ (**B**) can be prepared conveniently by the reaction of $\text{Fe}^{\text{III}}(\text{ClO}_4)_3 \cdot 9\text{H}_2\text{O}$ (1 mol) with sodium picolinate (3 mol) in water in 93% yield, followed by recrystallization with MeOH, changing it to the hydrous form, $\text{Fe}(\text{PA})_3(\text{H}_2\text{O})$ (**A**). By exposure to moisture in air, it exists as a mixture of the hydrous and anhydrous form in wet MeCN; ^{b)} Typical reaction procedure: to a solution of substrate (1 mmol) and $\text{Fe}(\text{PA})_3$ (0.5 mmol) in MeCN (70 ml) were added three 0.1s-ml portions of 30% aqueous H_2O_2 (0.3 ml, 3 mmol) every 30 min at room temperature and the reaction mixture was stirred for 3 h at room temperature. ^{c)} Isolated yields based on substrates (**1**). ^{d)} Trace amounts (<0.5%).

Chart 2. Proposed Active Species in $\text{Fe}^{\text{III}}(\text{PA})_3/\text{H}_2\text{O}_2/\text{MeCN}$ System

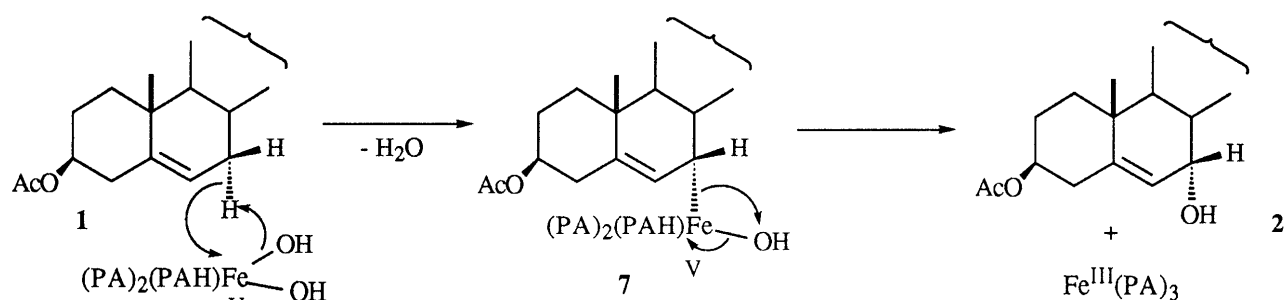


Chart 3. Proposed Mechanism for 7 α -Hydroxylation of Δ^5 -Steroids

The mechanism of stereoselective 7 α -hydroxylation for the formation of **2** can be postulated to be as follows (Chart 3). The σ bond formation between the C-7 α -position in **1** and Fe^V atom in (E) as a hypothetically active species with nonradical pathways³⁾ may take place stereoselectively to yield **7** under the stereoelectronic effect⁵⁾ and steric hindrance. Further, the cleavage of the σ bond between the Fe atom and the C7-position in **7** including the rearrangement of the hydroxy group, may proceed to permit **2** to retain its configuration. On the other hand, the possibility of participation of an active species Fe^V=O (**D**) in 7 α -hydroxylation cannot be excluded.

Subsequently, we investigated the reaction of **1a** with the Gif system (GoAgg^{III}; FeCl₃·6H₂O-PAH/H₂O₂/HOAc-pyridine) to compare it with the reaction with this modified system. Although reaction of **1a** with the above Gif reagent system gave only a 7-oxo derivative **4a** in 4% yield, it did not proceed for 7-hydroxy derivatives **2a** and **3a**. Furthermore, it was reported that the reactions of cholesterol acetate **1a** using known the allylic acetoxylation reagents, CuBr/*tert*-BuOOCOPh/HOAc,¹⁾ Pd(OAc)₂/Fe(NO₃)₃·9H₂O/O₂/HOAc,⁶⁾ and Pb(OAc)₄/HOAc⁷⁾ gave 3 β ,7 α - and 3 β ,7 β -diacetoxy-5-cholestene in almost same amount as the α and β forms, with about 20% yields.

These results provide a new example of oxidative 7 α -hydroxylation of Δ^5 -steroids, one of the major metabolic reactions catalyzed cytochrome P-450, in this model system for mono-oxygenase.

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