A New Electrochemical System for Stereoselective Allylic Hydroxylation of Cholesteryl Acetate with Dioxygen Induced by Iron Picolinate Complexes

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The oxygenation reaction of cholesteryl acetate 1 was examined with the $Fe^{III}(PA)_3/O_2$/MeCN system using an electrochemical method. The constant potential technique gave mainly the 7-hydroxylated product stereoselectively, along with the 7-oxo product. This oxygenation system is mechanistically unique, requiring iron catalyst, dioxygen, and both cathode and anode.

Key words allylic hydroxylation; iron catalysis; electrochemical oxidation; 7α-hydroxylation

Many investigations of oxygenation reactions using various chemical or electrochemical systems mimicking monooxygenase enzymes have been reported. Among these oxygenation models, studies on chemical systems using iron(III) picolinate ($Fe^{III}(PA)_3$) or iron(II) picolinate ($Fe^{II}(PA)_2$) complexes as catalysts have been reported under various conditions and in various solvents.[1—5] We are interested in stereoselective oxidation reactions, especially 7α-hydroxylation of 3β-acetoxy-Δ5-steroids, including cholesterol and oxysterols, from the viewpoints of their metabolism and biosynthesis.[6—8]

In the preceding paper, we reported a convenient oxidation system using $Fe^{III}(PA)_3/H_2O_2$/MeCN (acetonitrile) as an alternative to the chemical Gif model system ($GoAgg^{III}$), which is effective for stereoselective allylic hydroxylation of steroids.[9—11] However, hydrogen peroxide is potentially explosive, and is undesirable for large-scale reactions. On the other hand, the electrochemical method is useful for a variety of oxidations, because the redox potential can be controlled easily, and sometimes the reaction provides unique products and mechanisms. Recently Maki *et al.* have applied electrochemical methods to biomimetic oxidation systems.[12—14] We herein report new and unique electrochemical systems for oxygenation, particularly stereoselective allylic hydroxylation, involving the combination of $Fe^{III}(PA)_3/O_2$/MeCN [reagent system (A)] or $Fe^{II}(PA)_2/O_2$/MeCN [reagent system (B)] and electrolysis without hydrogen peroxide.

Results and Discussion

The reactions were conducted under similar conditions in all cases. Cholesteryl acetate (0.3 mmol) was dissolved in a 0.1 M solution of tetra *n*-butyl ammonium tetrafluoroborate as a supporting electrolyte in acetonitrile. The H-shaped one-compartment glass cell equipped with platinum mesh electrodes (cathode and anode) was filled with the above solution, and O_2 gas was bubbled through the mixture with magnetic stirring for 1 h at ambient temperature.

First, we investigated the reactions under constant current conditions. The results are summarized in Table 1 and Chart 1. The yields are isolated yields, and the ratios of **2**α:**2**β were calculated from the integration values in ^{1}H-NMR measurements of mixtures of the two isomers.[10,15] Runs 1 and 2 show the results of the electrochemical reaction of **1** with the reagent system (A) containing $Fe^{III}(PA)_3$ (0.06 mmol) as a catalyst. In the case of run 1, the 7-hydroxylated compound **2** was the major product (21% conversion yield), as in the oxygenation reaction with the $Fe^{III}(PA)_3/H_2O_2$/MeCN system mentioned above.[10] Increased current did not improve the yield, and caused decomposition of the substrate and products.

Table 1. Electrochemical Oxygenation of Cholesteryl Acetate (**1**) with Iron Complexes and Dioxygen in Acetonitrile under Constant Current Conditions

Run[a]	Iron catalyst	Current (mA)	Product (%)[b]				Ratio of **2**α:**2**β
			2[c]	**3**	**4**[c]	**1** (recovery)	
1	$Fe^{III}(PA)_3$	25	7.1 (21)	4.0 (12)	1.4 (4.2)	67	100 : 7
2	$Fe^{III}(PA)_3$	50	4.7 (4.9)	6.6 (6.9)	1.7 (1.8)	4.3	100 : 9
3	$Fe^{II}(PA)_2$	25	19 (27)	8.7 (12)	2.6 (3.6)	29	100 : 5
4	$Fe^{II}(PA)_2$	50	9.2 (9.3)	12 (13)	2.7 (2.7)	0.7	100 : 3
5	$Fe(ClO_4)_2$-PA-Py	25	2.9 (6.9)	4.7 (11)	2.1 (5.0)	58	100 : 8
6	$Fe(ClO_4)_2$-PA-Py	50	4.7 (6.7)	6.4 (9.1)	2.9 (4.1)	30	100 : 7

a) The reaction was run in a one-compartment cell. *b*) Isolated yield, and conversion yield are shown in parentheses. *c*) A mixture of α- and β-isomers.

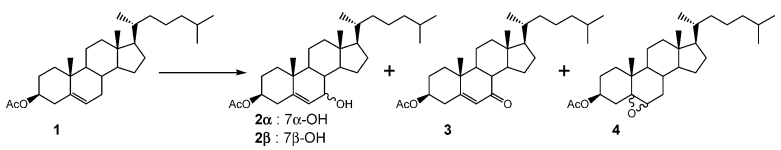

Chart 1. Oxygenation of Cholesteryl Acetate (**1**)

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Table 2. Electrochemical Oxygenation of Cholesteryl Acetate (**1**) with Iron Complexes and Dioxygen in Acetonitrile under Constant Potential Conditions

Run	Iron catalyst	Potential of working electrode	Product (%)[a]				Ratio of **2α**:**2β**
			2[b]	**3**	**4**[b]	**1** (recovery)	
7[c]	$Fe^{III}(PA)_3$	−0.1 V	21 (28)	11 (15)	Trace	26	100 : 8
8[c]	$Fe^{II}(PA)_2$	−0.1 V	29 (38)	14 (18)	Trace	24	100 : 7
9[c]	$Fe^{II}(ClO_4)_2$	−0.1 V	13 (19)	13 (19)	Trace	33	100 : 70
10[c]	$Fe^{III}(PA)_3$	—	No reaction	No reaction	No reaction		
11[c]	$Fe^{II}(PA)_2$	—	No reaction	No reaction	No reaction		
12[c,e]	$Fe^{III}(PA)_3$	−0.1 V	1.4	0.9	—	77	100 : 62
13[d]	$Fe^{III}(PA)_3$	−0.1 V	No reaction	No reaction	No reaction		
14[d]	$Fe^{III}(PA)_3$	+2.0 V	8.3	4.3	—	77	100 : 66
15[d]	—	+2.0 V	9.0	5.6	—	56	100 : 64
16[d]	$Fe^{III}(PA)_3$	+2.5 V	—	—	—	30	
17[d,f]	$Fe^{III}(PA)_3$	−0.1 V, then +2.0 V	12	1.5	Trace	52	100 : 19

a) Isolated yield, and conversion yield are given in parentheses. *b*) A mixture of α- and β-isomers. *c*) The reaction was run in the undivided cell. *d*) The reaction was run in the divided cell. *e*) The reaction was conducted under argon bubbling. *f*) The reaction time and conditions are different from those of other runs, see the text.

The electrochemical reaction with the reagent system (B) containing $Fe^{II}(PA)_2$ (0.06 mmol) as a catalyst gave similar results under constant current conditions with both 25 and 50 mA current, as shown in runs 3 and 4. The reagent system (B), prepared *in situ*, resulted in moderate yield (runs 5 and 6), but the 7-keto product **3** predominates in comparison with other systems. In all of these constant current reactions, the 7-hydroxylation showed α-preference (ratio of over 100 : 9).

Next, we investigated the reactions in the constant potential mode using a one-compartment cell under the following conditions. Since the redox potential of $Fe^{III}(PA)_3$ in acetonitrile was −0.08 V *vs.* Ag/AgCl, the cathode potential was set to −0.1 V. This potential is considered to be suitable, since it permits the one-electron reduction of $Fe^{III}(PA)_3$ in acetonitrile, and is not effective for reduction of dioxygen.[16] Other reaction conditions were similar to those in the constant current electrolysis reactions, and the results are summarized in Table 2.

The result of run 7 showed that the electrochemical reaction of **1** using reagent system (A) containing $Fe^{III}(PA)_3$ as a catalyst gave the 7-hydroxylated product **2** (21%) as the major product along with the ketone **3** (11%) and a trace amount of epoxide **4**. In the case of the electrochemical reaction using reagent system (B) containing $Fe^{II}(PA)_2$, a similar result was obtained (run 8). The hydroxylation in both runs 7 and 8 stereoselectively afforded the 7α-hydroxylated product in better yield than constant current conditions. When the iron(II) perchlorate, which lacks the PA moiety as a ligand, was used as a catalyst in run 9, the oxidation proceeded to give a product mixture of **2**, **3** and **4**, including the 7α-hydroxylated product **2α**, along with significant amount of the β-isomer **2β**. This result indicated that iron complex with PA as a ligand is essential for stereoselective 7α-hydroxylation.

In order to research the requirements for the reaction in runs 7 and 8, the following reactions were conducted. The reaction using reagent system (A) or (B) without electrolysis gave no product (runs 10 and 11). In run 12, when the electrochemical reaction was conducted using the reagent system (A) with bubbling of argon instead of O_2, the reaction did not proceed to any great extent.

On the other hand, in run 13, no reaction took place under similar conditions to run 7, but using a divided cell, in which the anode and the cathode compartments are separated with a glass filter. In contrast, the anodic reaction (+2.0 V *vs.* Ag/AgCl) of **1** using reagent system (A) in the divided cell afforded **2** (8.3%) and **3** (4.3%), but the stereoselectivity for **2α** was poor (run 14, **2α**:**2β**=100 : 66). This decreased stereoselectivity suggests that the oxygenation reaction in run 14 may proceed without the participation or influence of iron complex containing PA; in other words, substrate **1** is not oxidized by the iron complex generated from the electrolyses of the reagent system (A) or (B),[17] but rather, direct anodic oxidation may occur. In fact, in run 15, the direct anodic oxidation (+2.0 V *vs.* Ag/AgCl) of **1** with continuous bubbling of dioxygen gas in acetonitrile gave a similar result to run 14 in terms of product yields and stereoselectivity. Although increasing the potential caused a decrease of the recovered substrate **1**, no product such as **2** or **3** was formed in run 16. These results showed that direct anodic reaction of **1** could not give a similar result to run 7 or 8 in terms of the yield or stereoselectivity; in other words, our oxygenation system is different from direct anodic reaction.

Finally, in order to confirm the reaction sequence in our electrochemical oxygenation in run 7, the stepwise electrochemical reaction with reagent system (A) was carried out (run 17) under a constant potential condition in a divided cell. The procedure was carried out in the working electrode compartment of the divided cell, and the counter electrode compartment was filled with the solution of ammonium salt in acetonitrile.

Cathodic electrolysis at −0.1 V (*vs.* Ag/AgCl) of $Fe^{III}(PA)_3$ (1.0 equiv.) in acetonitrile was performed for 5 min with bubbling of argon gas. After the first electrolysis was stopped, O_2 was bubbled through the resulting reaction mixture, and then substrate **1** was added. The working electrode was switched to the anode, and the above acetonitrile solution containing the substrate **1** was subjected to anodic electrolysis at +2.0 V (*vs.* Ag/AgCl) with bubbling of argon gas for 15 min. These reactions finally afforded **2** (12%) stereoselectively as a major product, a result similar to those of runs 7 and 8. This result in run 17 provides some clues to the reaction mechanism of electrochemical oxygenation of **1**.

In the present electrochemical oxygenation using reagent systems (A) and (B), the precise mechanism remains to be investigated in detail, but some aspects of above results deserve comment. This oxygenation, including stereoselective

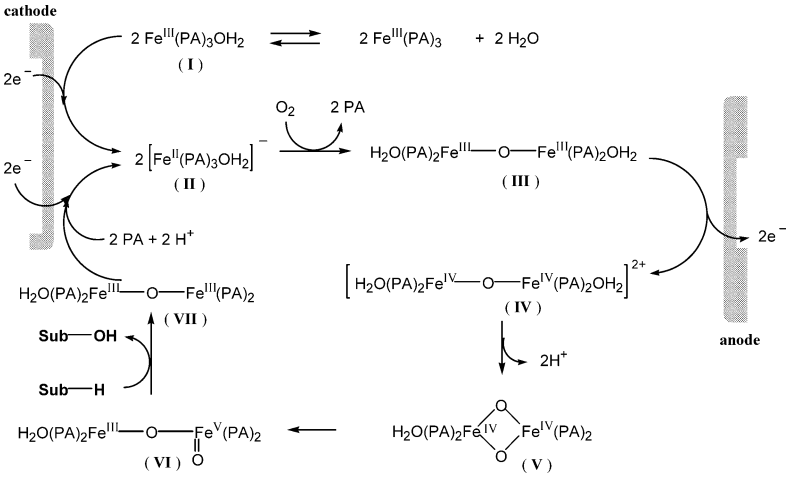

Chart 2. Proposed Mechanism for the Oxygenation of Cholesteryl Acetate

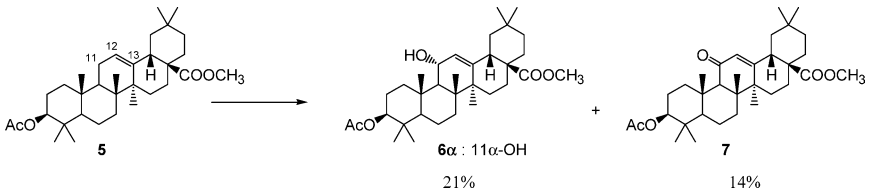

Chart 3. Oxygenation of Methyl 3-*O*-Acetyl-oleanolate (**5**)

allylic hydroxylation, did not proceed at all without electrolyses (both reduction and oxidation) or under conditions which omitted any one of the reagents, dioxygen or iron complex with PA as a ligand; in other words, the "$Fe^{III}(PA)_3$ or $Fe^{II}(PA)_2/O_2$/cathodic reduction/anodic oxidation" system as a whole is essential to promote the reaction. From this point of view, our electrochemical system is definitely different from the Gif-Orsay system[18,19] or the electrochemical system using both electrodes reported by Maki *et al.*[20]

A likely mechanism for the electrochemical oxygenation using system (A) is summarized in Chart 2. As we reported before, iron(III) picolinate is in an equilibrium of hydrated and anhydrous forms in acetonitrile. That is, in the first stage, the cathodic reduction of $Fe^{III}(PA)_3(H_2O)$ (**I**) to the Fe^{II} complex (**II**) take place. This is supported by the change in color from pale-yellow to deep-red. In the next step, dioxygen gas is adsorbed on the resulting iron complex **II**, which undergoes auto-oxidation by O_2 to form the iron μ-oxo-dimer, Fe^{III}–O–Fe^{III} complex.[21,22] This dioxygen adsorption was confirmed in another experiment using a gas burette, showing that 0.5 equivalent amount of dioxygen to iron catalyst was adsorbed. Subsequently, the anodic oxidation of complex **III** proceeds to yield the high valence species, the Fe^{IV}–O–Fe^{IV} complex (**IV**), in which water oxidation is induced by the Fe^{IV} atom, and ring closure proceeds to form the Fe_2-$\mu(O)_2$ complex (**V**) along with deprotonation.[23—26] After that, the ring cleavage of complex **V** results in the formation of the dimeric Fe^{III}–Fe^{V} manifold complex, $(H_2O)(PA)_2Fe^{III}$–O–Fe^{V}=O$(PA)_2$ (**VI**) as an active intermediate that can work as a monooxygenating species for **1**.[27,28] In the oxygenation of **1**, the oxygen source for hydroxyl and ketone formation at the C7 position in **2** and **3** is considered to be either dioxygen or water via complex **I**, though the details are not clear. The mechanism of stereoselective 7α-hydroxylation leading to the formation of **2**$\boldsymbol{\alpha}$ is analogous to that proposed by us for the oxygenation with the chemical system $Fe^{III}(PA)_3/H_2O_2$/MeCN.[10] Because the stereoselectivity of the 7-hydroxylation requires PA as a ligand, a steric effect can be considered as the main reason for the selectivity. After the oxygenation of **1** by complex **VI**, cathodic reduction of complex **VII** in the presence of PA and protons, which are generated by the former step, takes place to form complex **II** as the hydrated form. In the case of the electrochemical reaction with the reagent system (B), a similar mechanism can be proposed except for the first stage, *i.e.* the formation of Fe^{II} complex.

Finally, our electrochemical oxygenation using system (A) was applied to the reaction of methyl 3-*O*-acetyl-oleanolate (**5**). The reaction was run in constant potential manner, like run 7, and yielded the 11-α hydroxylated compound **6**$\boldsymbol{\alpha}$ (21%) stereoselectively without the formation of the β-isomer, and the ketone **7** (14%) (Chart 3). The yield of **6**$\boldsymbol{\alpha}$ was better than that of the oxidation using chemical system $Fe^{III}(PA)_3/H_2O_2$/MeCN, reported previously by us.[11]

Conclusion

We present a new method of stereoselective allylic hydroxylation using electrochemical method. This reaction is unique in the sense that it requires dioxygen, iron(III) picolinate complex and both anode and cathode.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO IR-700 spectrometer, and ^{1}H- and ^{13}C-NMR spectra with JEOL JNM-EX90, JNM-GX270, JNM-AL300, and JNM-GSX500 spectrometers, with tetramethylsilane as an internal standard ($CDCl_3$ solution). Chemical shifts are recorded in ppm, and coupling constants (*J*) are recorded in Hz. Mass spectra were recorded on a JEOL JMS-D300 spectrometer. Elemental analyses were performed on a Yanaco CHN-MT-3 apparatus and a Amco Flash EA 1112 instrument. Wako silica gel C-200 (200 mesh) and Merck Kieselgel 60 F_{254} were used for column chromatography and thin-layer chromatography (TLC), respectively. Preparative HPLC

(high-performance liquid chromatography) was carried out with a JASCO HPLC system (pump, JASCO 880; RI detector, JASCO 830) using a silica-3301-N (Senshu Pac, 8 f3300 mm i.d.) column.

Preparation of Iron(III) Picolinate Complexes Iron(III) perchlorate was a commercial product, used without further purification. Each iron complex was prepared as follows, and checked by elemental analysis.

$Fe^{III}(PA)_3 \cdot 4H_2O$ A solution of iron(III) perchlorate 9-hydrate (1.58 g, 3.3 mmol) in 10 ml of water was added to a solution of picolinic acid (1.23 g, 10 mmol) and sodium hydroxide (0.4 g, 10 mmol) in 10 ml of water with stirring at ambient temperature. The resulting pale yellow powder was collected by filtration and dried *in vacuo*. *Anal*. Calcd for $C_{18}H_{14}N_3O_7Fe$: C, 51.21; H, 2.87; N, 9.95; Found: C, 51.24; H, 3.01; N, 9.97.

$Fe^{III}(PA)_3$ The hydrated complex obtained as above was recrystallized from anhydrous acetonitrile, and pale green prisms were obtained mp 285—287 °C. *Anal.* Calcd for $C_{18}H_{12}N_3O_6Fe$: C, 49.12; H, 3.21; N, 9.55; Found: C, 49.97; H, 3.16; N, 9.52.

$Fe^{II}(PA)_2 \cdot 4H_2O$ A solution of iron(II) perchlorate hexahydrate (1.81 g, 5 mmol) in 10 ml of water was added to a solution of picolinic acid (1.23 g, 10 mmol) and sodium hydroxide (0.4 g, 10 mmol) in 10 ml of water[29,30] in an argon atmosphere using an AtmosBag. The resulting red-orange crystals were filtered under an argon stream, and used without further purification.

General Procedure for Electrochemical Reactions Cholesteryl acetate (0.3 mmol) and iron catalyst (0.06 mmol) in hydrated form were dissolved in a 0.1 M solution of tetra *n*-butylammonium tetrafluoroborate in 40 ml of acetonitrile. In the H-shaped glass cell equipped with platinum mesh electrodes (cathode and anode), this reaction mixture was electrolyzed under each condition with gas bubbling. After 1 h, the resulting mixture was poured into ice-water, and extracted with ether. The combined organic layer was washed with 10% hydrochloric acid, saturated sodium bicarbonate, and brine, then dried over magnesium sulfate, and filtered. The solvent was removed with an evaporator, and the residue was flash-chromatographed (ethyl acetate : hexane = 1 : 20), affording **3**, recovered **1**, a mixture of **2**α and **2**β, and a mixture of **4**α and **4**β were given. The product ratio of **2**α/**2**β was measured in terms of the integration ratio of the C7 proton peak. Further separation of these α/β products was performed with HPLC. Spectroscopic characteristics for each product were identical with those we reported before and those in the literature.[10,11] The characteristic ^{1}H-NMR signals are as follows:

2α: δ: 5.63 (1H, d, J=5.1, C6-H), 4.65 (1H, m, C3-H), 3.84 (1H, br-s, C7-H), 2.03 (3H, s, C3-OAc), 1.59 (3H, s, C19-H), 0.92 (3H, d, J=6.4, C21-H), 0.87 (3H, d, J=6.8, C27-H), 0.86 (3H, d, J=6.8 Hz, C26-H), 0.68 (3H, s, C18-H). IR (KBr) cm^{-1}: 3406, 1726, 1643. HR-MS *m/z*: 444.3648 (Calcd for $C_{29}H_{48}O_3$: 444.3604). LR-MS *m/z*: 444 (M^+).

2β: δ: 5.31 (1H, br-s, C6-H), 4.65, 3.84, 2.02 (3H, s, C3-OAc), 1.59 (3H, s), 0.92 (3H, s), 0.87 (3H, s), 0.86 (3H, s), 0.68 (3H, s). HR-MS *m/z*: 444.3653 (Calcd for $C_{29}H_{48}O_3$: 444.3604). LR-MS *m/z*: 444 (M^+).

3: δ: 5.70 (1H, d, J=1.6, C6-H), 4.71 (1H, m, C3-H), 2.05 (3H, s, C3-OAc), 1.21 (3H, s, C19-H), 0.92 (3H, d, J=6.4, C21-H), 0.87(3H, d, J=6.6, C27-H), 0.86 (3H, d, J=6.6, C26-H), 0.68 (3H, s, C18-H). IR (KBr) cm^{-1}: 1733, 1668. HR-MS, *m/z*: 442.3413 (Calcd for $C_{29}H_{46}O_3$: 442.3447). LR-MS *m/z*: 442 (M^+).

4α: δ: 5.00—4.91 (1H, m, C3-H), 2.89 (1H, d, J=4.4, C6-H), 2.01 (3H, s, C3-OAc), 1.07 (3H, s, C19-H), 0.89 (3H, d, J=6.7, C21-H), 0.87 (3H, d, J=6.7, C27-H), 0.86 (3H, d, J=6.7, C26-H), 0.61 (3H, s, C18-H). IR (KBr) cm^{-1}: 1726. HR-MS *m/z*: 444.3638 (Calcd for $C_{29}H_{48}O_3$: 444.3604). LR-MS *m/z*: 444 (M^+).

4β: δ: 4.81—4.71 (1H, m, C3-H), 3.08 (1H, d, J=2.4, C6-H), 2.03 (3H, s, C3-OAc), 1.00 (3H, s, C19-H), 0.89 (3H, d, J=6.8, C21-H), 0.86 (3H, d, J=6.5, C27-H), 0.85 (3H, d, J=6.5, C26-H), 0.64 (3H, s, C18-H). IR (KBr) cm^{-1}: 1726. HR-MS *m/z*: 444.3600 (Calcd for $C_{29}H_{48}O_3$: 444.3604). LR-MS *m/z*: 444 (M^+).

Electrochemical Reaction in Run 17 The working electrode compartment of the divided cell was filled with a solution of 44.0 mg (0.1 mmol) of iron catalyst in 20 ml of 0.1 M solution of *n*-butylammonium tetrafluoroborate in acetonitrile, and the counter electrode compartment was filled with 20 ml of a solution of 0.1 M electrolyte in acetonitrile. After the bubbling of argon for 10 min, electrolysis was done at −0.1 V for 5 min with argon bubbling, then stopped. The working electrode compartment of the divided cell was bubbled with dioxygen for 15 min, then the substrate **1** was added. After the bubbling of argon for 10 min, electrolysis was done at +2.0 V for 15 min with argon bubbling. The resulting mixture was poured into ice water, and extracted with ether. The combined organic layer was washed with 10% hydrochloric acid, saturated sodium bicarbonate, and brine, then dried over magnesium sulfate, and filtered. The solvent was removed with an evaporator, and the residue was flash-chromatographed (ethyl acetate : hexane = 1 : 20), affording **3** (1.5%), a trace amount of **4**, 52% recovery of **1**, and **2** (12%) as an α/β mixture (100 : 19).

Electrochemical Oxygenation Reaction of Methyl 3-*O*-Acetyl-oleanolate (5) Methyl 3-*O*-acetyl-oleanolate (**5**) (51.5 mg) and iron catalyst (0.02 mmol) were dissolved in 0.1 M solution of tetra *n*-butylammonium tetrafluoroborate in 40 ml of acetonitrile. In the H-shaped undivided glass cell, this reaction mixture was electrolyzed at −0.1 V with dioxygen gas bubbling. After 30 min, the resulting mixture was poured into ice-water, and extracted with ether. The combined organic layer was washed with 10% hydrochloric acid, saturated sodium bicarbonate, and brine, then dried over magnesium sulfate, and filtered. The solvent was removed with an evaporator, and the residue was flash-chromatographed (ethyl acetate : hexane = 1 : 20), affording **6**α (21%), **7** (14%), recovered **5** (22%), and trace amounts of 12,13-epoxide and 12-oxo compounds. The ^{1}H-NMR peaks were identical to those we reported before.[11]

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