Iron(III)Picolinate-Induced Oxygenation and Subsequent Rearrangement of Triterpenoid Derivatives with Hydrogen Peroxide

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The reaction of oleanane triterpenoid 1b with a Fe^{III}(PA; picolinate)$_3$/H_2O_2/MeCN system (reagent system A), a simple model system for mono-oxygenase, gave the 11α-hydroxyl derivative 3 as major product, along with 11-oxo derivative 4 and 12-oxo derivative 6. The reaction of lupane triterpenoid 2b with reagent system A gave only oxidative rearrangement compounds, (20*R*)-aldehyde 8 and (20*S*)-aldehyde 9 were epimeric isomers. Then, we have found that iron(III) picolinate complex, $Fe^{III}(PA)_3$ is efficient in effecting the rearrangement of triterpenoid epoxides 5 and 7 into the corresponding carbonyl compounds, 6, 8 and 9 with 1,2-shift of the hydride.

Key word oxygenation; methyl 3β-*O*-acetyl-oleanolate; betulin- diacetate; rearrangement; epoxide; iron(III) picolinate

Naturally occurring and semisynthetic triterpenoids including oleanane-type compound, 3-*O*-β-acetyl-oleanolic acid (**1a**) and lupane-type compound, betulin (**2a**) are reported to possess interesting biological, pharmacological, or medicinal activities similar to those of retinoids and steroids, such as anti-HIV (human immunodeficiency virus) activity and significant inhibitory activity against interferon-γ-induced nitric oxide production in mouse macrophages.[1] The biogenetic pathway to a variety of natural products of the triterpenoid series involves oxidations at positions adjacent to a double bond. Although apparently easily accomplished in many plant cells, this kind of transformation is often difficult in the laboratory.

Various reagents[2a—e] such as molecular oxygen, selenium dioxide and chromic acid have been used for effecting ketonization at the allylic position of triterpenoids, however, there have been only a few reports to date on direct allylic hydroxylation.[2f] The search for efficient reagents or methods for the preparation of stereoselective allylic alcohols continues unabated. Allylic hydroxylation of oleanane and lupane triterpenoids is interesting in terms of the synthesis to search out novel biologically active compounds and the biosynthesis of their triterpenoids.

Recently, we reported the modified system Fe(PA)$_3$/H_2O_2/MeCN (reagent system A), as an alternative to the Gif model system (GoAgg^{III}), which is effective for stereoselective 7α-hydroxylation of 3β-acetoxy-Δ^5 steroids.[3a,b] During further investigations to characterize this reagent system containing iron(III)picolinate [Fe(PA)$_3$] with hydrogen peroxide, we found that oxidation of methyl 3-*O*-acetyl-oleanolate (**1b**) utilizing reagent system A provided stereoselective 11α-hydroxy derivative **3** as major product, and $Fe^{III}(PA)_3$ promoted transformation of epoxides **5** and **7** into the corresponding carbonyl compounds, **6**, **8** and **9** *via* 1,2-shift of the hydride. We herein deal with the oxygenation of triterpenoid derivatives **1b** and **2b** utilizing reagent systems A and $Fe^{III}(ClO_4)_3 \cdot 9H_2O$–picolinic acid (PAH)–pyridine (Py)/H_2O_2/acetic anhydride (Ac_2O)–MeCN system (reagent system B), and $Fe^{III}(PA)_3$-induced rearrangement reaction of epoxides **5** and **7**.

Crystals of $Fe^{III}(PA)_3$,[3b,4] the iron(III)–picolinate complex used in reagent system A can be prepared conveniently by reaction of $Fe(ClO_4)_3 \cdot 9H_2O$ with sodium picolinate. The iron(III)picolinate complex in reagent system B, on the other hand, was used as a solution of components in place of the complex itself in the reagent system A. In a preceding paper,[3b] we reported that reagent systems A and B differ in reactivity which may be due to structural differences between the dimeric Fe^{III}–Fe^{V} manifold complex and the monomeric Fe^{V} complexes as intermediate active species, generated by reaction between $Fe^{III}(PA)_3$ or $Fe^{III}(PA)_3(H_2O)$ and H_2O_2 or AcOOH (prepared from the reaction between H_2O_2 and Ac_2O).

Methyl 3-*O*-acetyl-oleanolate (**1b**) and 3β,28-di-*O*-acetyl-betulin (**2b**) were prepared as follows: From the $CHCl_3$ extract of the bark (*Betula platyphylla* SUKATCHEV var. *japonica* HARA, Shirakanba in Japanese) collected in June, 3-*O*-acetyl-oleanolic acid (**1a**) and betulin (**2a**) were isolated together with a few other compounds. Their structures were confirmed by comparison of the physical properties and spectral data with those previously reported.[5] Methyl oleanolate **1b** was obtained by methylation of **1a** with 10% trimethylsilyldiazomethane in *n*-hexane, and betulin acetate **2a** using Ac_2O/pyridine was acetylated to give the *O*-acetyl derivative **2b**.[6]

First, oxidation of **1b** with reagent system A was carried out to give stereoselective 11α-hydroxy derivative **3** (19.2%) at the allylic position as major product, along with 11-oxo derivative **4** (6.8%), 12-oxo derivative **6** (9.3%) with the 13β-configuration, and recovered material **1b** (51.3%) as shown in Table 1. Although the formation of the epoxide **5** was not observed in this reaction, compound **6** may be formed by epoxidation of **1b** followed by rearrangement of the resulting epoxide **5** as described below. Subsequently, oxidation of **1b** with reagent system B gave **6** (38.4%) as major product without the formation of **3**, and **4** (17.6%) along with a few other compounds which could not be isolated. This different reactivity of reagent system A in comparison with reagent system B may be due to structural differences between intermediate iron complexes[3b] generated from these reagent systems as described above. We then investigated the reaction of **1b** with the Gif system (GoAgg^{III}) to compare with the present reagent system A. However, the formation of 11-hydroxy derivative **3** was not observed in this case.

The structural identification of **3**[7] and **4**[8] was made by comparing the physical data of the corresponding com-

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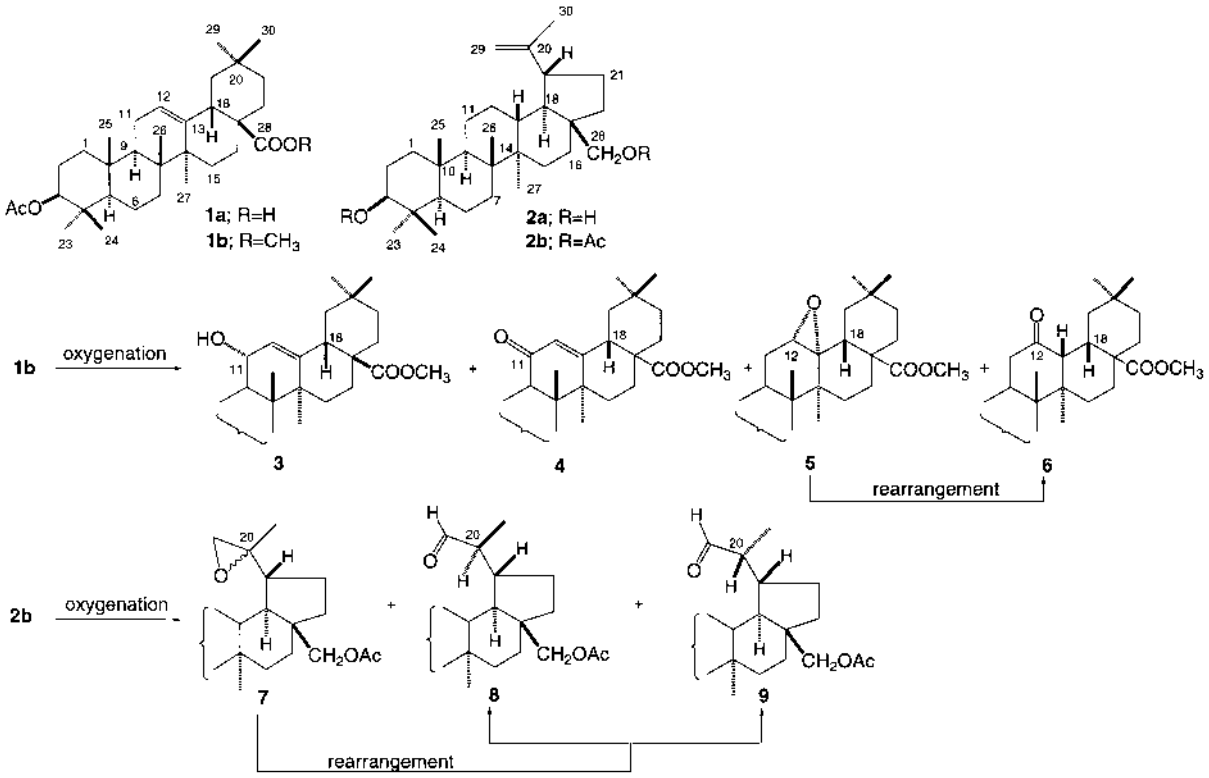

Chart 1

Table 1. Oxygenation of Triterpenoids **1b** and **2b** with Various Reagent Systems

Run	Substrate	Reagent	Product (yield, %)[g]			Recovery (%)
1	**1b**	Reagent system A[a]	**3** (19.2)	**4** (6.8)	**6** (9.3)	**1b** (51.3)
2	**1b**	Reagent system B[b]	**4** (17.6)	**6** (38.4)		**1b** (0.0)
3	**1b**	Reagent system C[c]	**4** (4.7)	**6** (12.8)		**1b** (48.1)
4	**1b**	Reagent system D[d]	**4** (trace)[h]	**6** (trace)		**1b** (92.6)
5	**1b**	Gif system ($GoAgg^{III}$)[e]	**4** (6.1)			**1b** (80.9)
6	**1b**	MCPBA[f]	**5** (55.0)			**1b** (0.0)
7	**2b**	Reagent system A	**8** (15.0)	**9** (29.8)		**2b** (41.4)
8	**2b**	Reagent system B	**7** (37.8)	**8** (5.3)	**9** (4.1)	**2b** (37.8)
9	**2b**	MCPBA	**7** (85.0)			**2b** (0.0)

a) $Fe(PA)_3/H_2O_2$/MeCN. *b*) $Fe(ClO_4)_3 \cdot 9H_2O$–PAH–Py/H_2O_2/Ac_2O–MeCN. *c*) $Fe(PA)_3$/AcOOH/MeCN. *d*) $Fe(ClO_4)_3 \cdot 9H_2O$–PAH–Py/H_2O_2/MeCN. *e*) $FeCl_3 \cdot 6H_2O$–PAH/H_2O_2/AcOH–Py. *f*) *m*-Chloroperoxybenzoic acid. *g*) Isolated yields after silica gel column chromatography followed by HPLC. *h*) Trace amounts (<0.5%).

pounds with the respective authentic samples. The planar structure of **6** was elucidated by the analyses of IR, ^{1}H- and ^{13}C-NMR spectra, with the aid of 2D NMR spectral analyses,[9] and comparison of physical data with those of the authentic sample.[10a] The stereochemistry of C_{13}-H in **6** was established by direct identification of ^{13}C-NMR data with those of an authentic sample,[10] and analyses of the vicinal coupling constant between C_{13}-H and C_{18}-H in ^{1}H-NMR spectrum. In the ^{13}C-NMR spectrum of **6** in $CDCl_3$, carbon signals observed at δ 211.61 (C_{12}) and δ 51.85 (C_{13}) were closely similar to those (δ 210.8 and δ 51.7) of an authentic sample, 12-oxo derivative **6** having 13β-configuration. In the ^{1}H-NMR spectrum of **6** in $CDCl_3$, the proton signal of C_{13}-H (δ 2.610) showed a small coupling constant ($J_{13,18}$=4.27 Hz). These observations clearly suggested that compound **6** must be 12-oxo derivative with 13β- and 18β-configurations.

We next investigated the reaction of **2b** with the reagent system A. However, the expected allyic hydroxylation of **2b** did not proceed in this case. This reaction gave epimeric isomers, (20*R*)-aldehyde **8** (15.0%) and (20*S*)-aldehyde **9** (29.8%) together with recovered starting material **2b** (41.4%). Subsequently, reaction of **2b** with reagent system B afforded a mixture of 20,29-α and β epoxides **7** (37.8%) as major product along with **8** (5.3%) and **9** (4.1%). The structures of **7**, **8**, and **9** were identified by direct comparison of the physical data with reported values.[11,12]

The reaction mechanism for formations of **3**, **4**, and **7** may be analogous to those we previously proposed.[3b] The stereoselective formation process of 11α-hydroxy derivative **3** may be similar to that of the previously reported 7α-hydroxylation of 3β-acetoxy-Δ^5 steroids[3a,b] with reagent system A. Farina and Pinza[10a] reported earlier that 12α,13α-epoxide **5** and 12β,13β-epoxide were converted under acidic condition ($BF_3 \cdot Et_2O$, *etc.*) into the more stable 12-oxo derivative **6** with 13β-configuration. It was also reported that iron (III)-tetraphenylporphyrin, $Fe(TPP)ClO_4$, act as an effective Lewis

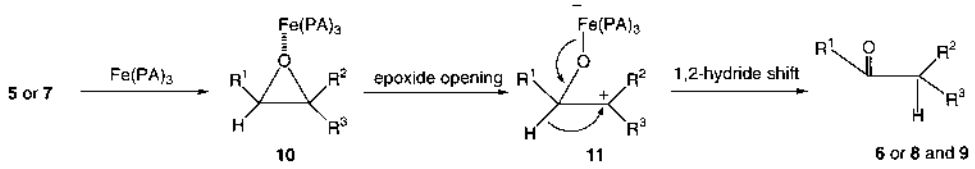

Chart 2. Proposed Mechanism for the Formations of **6** or **8** and **9** through the Expoxide **5** or **7**

Table 2. Rearrangement of Epoxides **5** and **7** with Various Reagents[a)]

Run	Substrate	Reagent	Product (yield, %)[f)]	Recovery (%)
1	**5**	Reagent system A[b)]	**6** (71)[g)]	**5** (trace)
2	**5**	Reagent system B[c)]	**6** (45)	**5** (50)
3	**5**	$Fe(PA)_3$	**6** (93)[g)]	**5** (trace)
4	**5**	H_2O_2/Ac_2O	**6** (trace)[h)]	**5** (95)
5	**5**	—[d)]	**6** (trace)	**5** (95)
6	**5**	$Fe(ClO_4)_3\cdot 9H_2O$[e)]	**6** (50)	**5** (0)
7	**7**	Reagent system A	**8**+**9** (42)[i)]	**7** (trace)
8	**7**	Reagent system B	**8**+**9** (trace)	**7** (95)
9	**7**	$Fe(PA)_3$	**8**+**9** (60)	**7** (trace)
10	**7**	$Fe(ClO_4)_3\cdot 9H_2O$–PAH–Py	**8**+**9** (trace)	**7** (95)
11	**7**	H_2O_2	—	**7** (100)
12	**7**	—[d)]	—	**7** (100)

a) These reactions were carried out for 3 h at room temperature using acetonitrile (MeCN) as solvent in all cases. *b*) $Fe(PA)_3/H_2O_2$/MeCN. *c*) $Fe(ClO_4)_3\cdot 9H_2O$–PAH–Py/H_2O_2/Ac_2O–MeCN. *d*) This reaction was carried out without reagent in MeCN (the blank test). *e*) This reaction gave **6** along with another product of which structure was not assigned. *f*) Yields were determined by GLC analysis. *g*) Isolated yields by silica gel column chromatography. *h*) Trace amounts (<0.5%). *i*) Yield of a mixture of **8** and **9**.

acid catalyst for the rearrangement of the epoxides into the corresponding ketones.[13)]

The above information allows some suggestions on the mechanism of formation of the carbonyl compounds **6**, **8**, and **9**; it can be postulated as follows (Chart 2). In a preceding paper[3b)] we reported that by exposure to moisture in air, the iron(III) picolinate complex exists as a mixture of the anhydrous form, $Fe(PA)_3$ and the hydrous form, $Fe(PA)_3(H_2O)$ in wet MeCN in equilibrium. In addition, the six coordinated anhydrous form, $Fe(PA)_3$ is transformed to the seven coordinated monohydrate complex, $Fe(PA)_3(H_2O)$ by the addition of a small amount of water in MeCN, and is changed to the inactive bridged-dimer, $[(PA)_2Fe(OH)_2]$[3b)] by addition of a large amount of water. The iron(III) picolinate complex in reagent system A exists as the anhydrous form. However, the iron complex in reagent system B is transformed gradually to $[(PA)_2Fe(OH)_2]$[3b)] from $Fe(PA)_3$ *via* $Fe(PA)_3(H_2O)$ by the effect of H_2O contained in $Fe(ClO_4)_3\cdot 9H_2O$ with the elapse of time. In these iron complexes, $Fe(PA)_3$ may work as the most effective Lewis acid catalyst for the rearrangement of the epoxides **5** or **7**. That is, coordination of $Fe(PA)_3$, to epoxide **5** or **7** derived from oxygenation of **1b** or **2b** is followed by the regioselective cleavage of the C–O bond to give the most stable tertiary-carbocation **11** which is transformed into ketone **6** or aldehydes **8** and **9** *via* 1,2-shift of the hydride.

This speculation is strongly supported by the results of the following reactions of 12α,13α-epoxide **5** and a mixture of 20,29-α and β epoxides **7**, prepared from the reactions of **1b** and **2b** with *m*-chloroperoxybenzoic acid, under various conditions as shown in Table 2. The structure of **5** was confirmed by 2D-NMR spectral analyses.

The reaction of **5** with $Fe^{III}(PA)_3$ in MeCN gave only the corresponding rearrangement product **6** in excellent yield (run 3). Similar reaction with reagent system A gave only **6** (run 1). Reactions with H_2O_2/Ac_2O in MeCN, or without reagents which do not have $Fe^{III}(PA)_3$ were examined, but transformation rarely occurred (runs 4 and 5). Although the reaction with $Fe(ClO_4)_3\cdot 9H_2O$ in MeCN proceeded rapidly, compound **6** and another product of which structure was not assigned, were obtained (run 6). On the other hand, reaction of **7** with $Fe(PA)_3$ in MeCN also gave the corresponding rearrangement products **8** and **9** in 60% yield (run 9). Reactions hardly occurred with reagent system B and $Fe(ClO_4)_3\cdot 9H_2O$–PAH–Py/MeCN system or without reagents (runs 8, 10, and 12).

In these rearrangement reactions, the best results were obtained with both **5** and **7** by reaction using $Fe(PA)_3$. The different yield of reagent system A in comparison with reagent system B may be due to quantitative differences of $Fe(PA)_3$ contained in these reagents, although the details are not clear.

In conclusion, these results indicated that the iron complex

Table 3. ^{13}C-NMR Spectral Data for **1b**, **3**—**6**[a)]

C-atom	**1b**	**3**	**4**	**5**	**6**
C1	38.11	39.82	38.78	38.38	37.66
C2	23.40	23.61	23.58	23.60	23.41
C3	80.92	80.69	80.63	80.70	80.45
C4	39.28	37.88	38.05	37.65	37.76
C5	55.31	55.30	55.09	55.21	55.19
C6	18.21	18.31	17.30	17.84	18.19
C7	32.60	33.03	32.88	34.04	31.77
C8	37.68	43.06	43.48	39.24	41.26
C9	47.55	56.59	61.69	43.76	49.64
C10	36.93	37.99	37.13	36.59	36.84
C11	23.52	67.28	200.24	23.84	38.50
C12	122.26	125.57	127.98	67.27	211.61
C13	143.80	148.30	168.72	63.65	51.85
C14	41.64	41.86	45.05	40.32	41.86
C15	27.67	27.75	27.74	29.32	27.56
C16	23.06	22.91	23.44	22.67	22.76
C17	46.72	46.32	46.32	47.77	47.37
C18	41.30	40.57	41.60	40.85	31.99
C19	45.85	45.51	44.23	38.01	36.20
C20	30.68	30.71	30.68	30.36	30.65
C21	33.86	33.77	33.71	34.04	34.48
C22	32.37	32.17	31.60	32.59	32.96
C23	28.03	28.09	28.07	28.21	27.91
C24	16.66	16.82	16.68	16.95	16.46
C25	15.34	16.62	16.24	16.58	15.26
C26	16.83	18.31	18.94	19.91	16.13
C27	25.88	26.28	22.95	22.67	20.56
C28	178.27	178.08	177.53	178.38	178.41
C29	33.09	33.03	32.83	33.20	33.39
C30	23.63	23.58	23.53	23.40	23.17
C3-O$\underline{C}$O	170.98	170.97	171.03	170.91	170.91
C3-OCO$\underline{CH_3}$	21.28	21.33	21.32	21.30	21.27
C17-COO$\underline{CH_3}$	51.49	51.67	51.90	51.72	51.80

Assignment based upon ^{1}H–^{13}C COSY and HMBC experiments. *a*) δ in $CDCl_3$; ^{13}C-NMR at 125.65 MHz.

Table 4 ^{13}C-NMR Spectral Data for **2b**, **7**—**9**[a)]

C-atom	**2b**	**7**	**8**	**9**
C1	38.36	38.41	38.39	38.37
C2	23.69	23.68	23.65	23.67
C3	80.90	80.87	80.82	80.87
C4	37.77	37.80	37.79	37.79
C5	55.35	55.37	55.28	55.33
C6	18.14	18.16	18.14	18.14
C7	34.09	34.12	34.14	34.15
C8	40.86	40.91	40.91	40.90
C9	50.25	50.14	49.82	49.87
C10	37.03	37.06	37.02	37.03
C11	20.76	20.91	20.76	20.64
C12	27.02	26.80	27.53	26.52
C13	37.53	36.71	37.19	37.23
C14	42.66	42.68	42.79	42.89
C15	27.92	26.82	26.85	26.86
C16	29.54	29.74	29.69	29.79
C17	46.27	46.68	46.35	46.17
C18	48.74	49.72	49.23	49.67
C19	47.69	46.14	42.65	37.13
C20	150.13	60.01	48.86	47.52
C21	29.71	25.86	24.71	23.42
C22	34.52	34.38	34.26	34.89
C23	27.92	27.94	27.93	27.93
C24	16.47	16.49	16.50	16.49
C25	16.14	16.15	16.08	16.08
C26	16.00	16.01	16.00	16.00
C27	14.70	14.61	14.53	14.52
C28	62.79	62.51	62.09	62.42
C29	109.87	57.16	206.44	204.44
C30	19.09	18.09	14.45	14.54
C3-O<u>CO</u>	171.01	171.04	170.95	171.00
C3-OCO<u>CH$_3$</u>	21.31	21.33	21.29	21.30
C28-O<u>CO</u>	171.63	171.50	171.53	171.49
C28-OCO<u>CH$_3$</u>	21.04	21.03	20.99	20.99

Assignment based upon ^{1}H–^{13}C COSY and HMBC experiments. *a*) δ in $CDCl_3$; ^{13}C-NMR at 125.65 MHz.

$Fe^{III}(PA)_3$ is not only a mild and characteristic catalyst for stereoselective 11α-hydroxylation at allylic position of oleanane triterpenoid, but also for the transformation of the epoxides in oleanane and lupane triterpenoids into the corresponding carbonyl compounds.

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). Mass spectra were recorded on a JEOL JMS-D300 spectrometer. Elemental analyses were done using a Yanaco CHN-MT-3 apparatus. Wako silica gel C-200 (200 mesh) and Merck Kieselgel 60 F_{254} were used for column chromatography and thin-layer chromatography (TLC), respectively. Each organic extract was dried over Na_2SO_4. 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 Pak, 8ϕ×300 mm i.d.) column. GLC-MS data were obtained with a Shimadzu QP-5000 spectrometer. GLC analysis was carried out with a Shimadzu GC-380 gas chromatograph.

Isolation of 1a and 2a The bark (2 kg) of *Betula platyphylla* var. *japonica* was extracted with $CHCl_3$ at room temperature. The extract (170 g) was dissolved with ether and the resulting solution was concentrated to a syrup under reduced pressure. The residue was subjected to preparative HPLC on YMC-GEL (SIL-120-s-50) using ether–$CHCl_3$ (50 : 50, v/v). The first eluate gave 3.6 g (0.18%) of 3β-*O*-acetyl-18β-oleanolic acid (**1a**) as colorless needles, mp 268—269 °C (MeOH). The second eluate gave 14.5 g (0.75%) of betulin (**2a**) as colorless needles, mp 248—250 °C (EtOH). **1a**: MS *m/z*: 498 (M^+). *Anal*. Calcd for $C_{32}H_{50}O_4$: C,77.06; H, 10.11. Found: C,77.09; H, 10.22. **2a**: MS *m/z*: 442 (M^+). *Anal*. Calcd for $C_{30}H_{50}O_2$: C, 81.39; H, 11.38. Found: C, 81.55; H, 11.40.

Methylation of 1a A solution of 10% trimethylsilyldiazomethane in *n*-hexane (11.31 g, 9.90 mmol) was added dropwise to a stirred solution of **1a** (4.06 g, 8.15 mmol) in benzene (100 ml) and methanol (15 ml) at room temperature and the mixture was stirred for 2 h. After acetic acid (0.5 ml) was added to the resulting reaction mixture, the solvent was removed under vacuum to yield a colorless oil (4.49 g) which was flash chromatographed over silica gel eluted with AcOEt–hexane (1 : 20, v/v) to give 3.37 g (81%) of methyl 3-*O*-acetyl-18β-oleanolate (**1b**), colorless needles (EtOH), mp 229—230 °C. **1b**: IR (KBr) cm^{-1}: 1726. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.72 (3H, s, C26-H), 0.85 (3H, s, C23-H), 0.86 (3H, m, C24-H), 0.89 (3H, s, C29-H), 0.925 (3H, s, C30-H), 0.929 (3H, s, C25-H), 0.97—2.01 (complex, CH_2 and CH), 1.13 (3H, s, C27-H), 2.04 (3H, s, –OCOCH$_3$), 2.86 (1H, dd, *J*=4.59, 13.96 Hz, C18β-H), 3.62 (3H, s, –COOCH$_3$), 4.49 (1H, t, *J*=8.08 Hz, C3α-H), 5.28 (1H, d, *J*=3.86 Hz, C12-H). MS *m/z*: 512 (M^+). *Anal*. Calcd for $C_{33}H_{52}O_4$: C, 72.29; H, 10.22. Found: C, 72.40; H, 10.30.

Acetylation of 2a A solution of betulin **2a** (1.93 g, 4.35 mmol) in anhydrous pyridine (15 ml) was treated with Ac_2O (3.5 ml) and stirred for 6 h. The reaction mixture was diluted with EtOAc, and washed with 10% HCl and saturated $NaHCO_3$. The organic layer was dried and concentrated under vacuum to give 2.15 g (94%) of 3β,28-di-*O*-acetyl-betulin (**2b**), a colorless powder, mp 222—224 °C (MeOH). **2b**: IR (KBr) cm^{-1}: 2948, 2870, 1736, 1640, 1243. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.835 (3H, s, C25-H), 0.845 (3H, s, C24-H), 0.97 (3H, s, C23-H), 1.03 (3H, s, C26-H), 1.68 (3H, s, C20-Me), 2.04 (3H, s, OCOCH$_3$), 2.07 (3H, s, OCOCH$_3$), 2.44 (1H, dt, *J*=5.8, 10.8 Hz, C19-H), 3.85 (1H, br d, *J*=11.0 Hz, C28-H), 4.24 (1H, br d, *J*=11.0 Hz, C28-H), 4.47 (1H, dd, *J*=6.1, 10.1 Hz, C3-H), 4.59 (1H, br s, C29-H), 4.68 (1H, br s, C29-H). MS *m/z*: 526 (M^+). *Anal*. Calcd for $C_{34}H_{54}O_4$: C, 77.52; H, 10.33. Found: C, 77.58; H, 10.28.

Procedure for Oxygenation of 1b with the $Fe(PA)_3/H_2O_2$/MeCN System (Reagent System A) Three 0.1-ml portions of 30% aqueous H_2O_2 solution (0.3 ml, 3 mmol) were added dropwise every 30 min to a vigorously stirred solution of **1b** (512 mg, 1 mmol) and $Fe(PA)_3$ (211 mg, 0.5 mmol) in MeCN (70 ml) at room temperature and the reaction mixture was then stirred for 3 h. The reaction mixture was poured into ice water and extracted with ether. The organic layer was washed with saturated Na_2SO_3, $NaHCO_3$, and brine. The ethereal solution was dried and concentrated and the residue purified by column chromatography on silica gel with hexane–AcOEt (10 : 1, v/v). The first eluate gave 262.5 mg (51.3%) of recovered starting material **1b**. The second eluate gave a mixture of **4** and **6**. The third eluate gave 101.5 mg (19.2%) of methyl 3β-*O*-acetyl-11α-hydroxy-18β-oleanolate **3**, colorless crystals (methanol), mp 202—205 °C (MeOH). The mixture of **4** and **6** was further subjected to preparative HPLC with hexane–AcOEt (10 : 1, v/v). The first eluate afforded 36 mg (6.8%) of methyl 3β-*O*-acetyl-11-oxo-18β-oleanolate (**4**), colorless crystals (EtOH), mp 250—252 °C. The second eluate afforded 49 mg (9.3%) of methyl methyl 3β-*O*-acetyl-11-dehydro-12-oxo-18β-oleanolate (**6**), colorless crystals (methanol), mp 195—198 °C. Analysis by GLC-MS and GLC confirmed the formation of **1b** (retention time (rt), 12.32 min), **3** (rt, 20.43 min), **4** (rt, 23.85 min), and **6** (rt, 28.35 min). **3**: IR (KBr) cm^{-1}: 3428, 1722. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.74 (3H, s, C26-H), 0.867 (3H, s, C23-H), 0.870 (3H, m, C24-H), 0.91 (3H, s, C29-H), 0.94 (3H, s, C30-H), 1.04 (3H, s, C25-H), 1.05—2.30 (complex, CH_2 and CH), 1.22 (3H, s, C27-H), 2.04 (3H, s, –OCOCH$_3$), 2.87 (1H, dd, *J*=3.9, 13.9 Hz, C18β-H), 3.63 (3H, s, –COOCH$_3$). 4.19 (1H, dd, *J*=4.3, 8.7 Hz, C11β-H), 4.51 (1H, dd, *J*=12.1, 3.0 Hz, C3α-H), 5.34 (1H, d, *J*=4.0 Hz, C12-H). $[\alpha]_D^{25}$ +39.92° (*c*=1.0, $CHCl_3$). MS *m/z*: 528 (M^+). HR-MS Calcd for $C_{33}H_{52}O_5$: 528.3815. Found: 528.3809. *Anal*. Calcd for $C_{33}H_{52}O_5$: C,74.96; H, 9.91. Found: C, 74.90; H, 9.96. **4**: IR (KBr) cm^{-1}: 2944, 2868, 1726, 1662. ^{1}H-NMR ($CDCl_3$) δ: 0.87 (6H, s, C23 and 24-H), 0.91 (3H, s, C25-H), 0.93 (3H, s, C29-H), 0.94 (3H, s, C30-H), 1.13 (3H, s, C26-H), 1.36 (3H, s, C27-H), 2.05 (3H, s, –OCOCH$_3$), 2.34 (1H, s, C9α-H), 2.83 (1H, dt, *J*=3.67, 13.42 Hz, C19-H), 3.00 (1H, dd, *J*=3.35, 13.73 Hz, C18β-H), 3.63 (3H, s, –COOCH$_3$). 4.51 (1H, dd, *J*=4.88, 11.60 Hz, C3α-H), 5.64 (1H, s, C12-H). $[\alpha]_D^{20}$ +53.58° (*c*=1.0, $CHCl_3$). MS *m/z*: 526 (M^+). HR-MS Calcd for $C_{33}H_{50}O_5$: 526.3658. Found: 526.3658. *Anal*. Calcd for $C_{33}H_{50}O_5$: C,75.24; H, 9.57. Found: C,75.22; H, 9.69. **6**: IR (KBr) cm^{-1}: 2948, 1724, 1700, 1242. ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 0.833 (1H, dd, *J*=1.83, 11.59 Hz, C5-H), 0.860 (3H, s, C24-H), 0.867 (3H, s, C23-H), 0.876 (3H, s, C25-H), 0.903 (3H, s, C29-H), 0.939 (3H, s, C27-H), 0.962 (3H, s, C26-H), 0.975 (3H, s, C30-H), 1.009 (1H, dd, *J*=4.27, 13.12 Hz, C1-H), 1.075 (1H, ddd, *J*=1.53, 4.27 Hz, 13.42 Hz, C15-H), 1.181—1.266 (2H, m, C19- and C21-H), 1.298—1.360 (2H, m, C7- and C21-H), 1.397—1.528 (2H, m, C7- and C22-H), 1.535—1.596 (1H, m, C1-H), 1.623—1.671 (7H, m, C2-, C6-,

C9-, C15-, and C16-H), 1.794 (1H, dt, J=4.58, 13.74 Hz, C22-H), 1.879 (1H, m, C16-H), 1.937 (1H, m, C19-H), 2.042 (3H, s, –OCOCH$_3$), 2.135 (1H, dd, J=13.12, 16.79 Hz, C11-H), 2.230 (1H, dd, J=5.19, 16.79 Hz, C11-H), 2.610 (1H, d, J=4.27 Hz, C13-H), 2.791 (1H, dt, J=4.27, 13.42 Hz, 18-H), 3.676 (3H, s, –COOCH$_3$), 4.471 (1H, dd, J=4.58, 11.30 Hz, C3-H). $[\alpha]_D^{25}$ −6.54° (c=1.0, CHCl$_3$). MS m/z: 528 (M$^+$). HR-MS Calcd for $C_{33}H_{52}O_5$: 528.3815. Found: 528.3812. *Anal*. Calcd for $C_{33}H_{52}O_5$: C, 74.96; H, 9.91. Found: C, 74.85; H, 9.80.

With Fe(ClO$_4$)$_3$·9H$_2$O-PAH-Py/H$_2$O$_2$/Ac$_2$O-MeCN (Reagent System B) Three 0.1-ml portions of 30% aqueous H_2O_2 solution (0.3 ml, 3 mmol) were added dropwise to a solution of Fe(ClO$_4$)$_3$·9H$_2$O (258 mg, 0.5 mmol), picolinic acid (185 mg, 1.5 mmol), pyridine (197.5 mg, 2.5 mmol), and **1b** (512 mg, 1 mmol) in MeCN (70 ml) and Ac_2O (1 ml) at room temperature with vigorous stirring, and the whole was stirred for 3 h. The reaction mixture was worked up according to the procedure described for the oxygenation of **1b** with reagent system A. Analysis by GLC-MS and GLC confirmed the formation of **4** and **6**. Yields are listed in Table 1.

With Fe(PA)$_3$/AcOOH/MeCN (Reagent System C) A mixture of 0.5 ml of acetic acid, 0.5 ml of 30% aqueous H_2O_2 and catalytic amount of concentrated sulfuric acid was stirred at 0 °C for 30 min. To a stirred solution of **1b** (256 mg, 0.50 mmol) and Fe(PA)$_3$ (110 mg, 0.25 mmol) in MeCN (35 ml) at room temperature, the AcOOH solution prepared as above was added, followed by stirring for 24 h. The reaction mixture was worked up according to the previous procedure. Analysis by GLC-MS and GLC confirmed the formation of **4** and **6**. Yields are listed in Table 1.

With Fe(ClO$_4$)$_3$·9H$_2$O-PAH-Py/H$_2$O$_2$/MeCN (Reagent System D) Three 0.1-ml portions of 30% aqueous H_2O_2 solution (0.3 ml, 3 mmol) were added dropwise to a solution of Fe(ClO$_4$)$_3$·9H$_2$O (258 mg, 0.5 mmol), picolinic acid (185 mg, 1.5 mmol), pyridine (197.5 mg, 2.5 mmol), and **1b** (512 mg, 1 mmol) in MeCN (70 ml) at room temperature with vigorous stirring, and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was worked up according to the procedure described for reagent system A. Analysis by GLC-MS and GLC confirmed the formation of **4** and **6**. Yields are listed in Table 1.

With FeCl$_3$·6H$_2$O/H$_2$O$_2$/AcOH-Py (GoAgg^{III}) This reaction was carried out by the procedure reported previously by Barton and Doller.[14] Analysis by GLC-MS and GLC confirmed the formation of **4**. Yields are listed in Table 1.

Procedure for Oxidation of 2b with Reagent System A This reaction was carried out at room temperature for 2 h according to the general procedure used for rearrangement reaction of **1b** with reagent system A. The crude product was purified by column chromatography on silica gel with hexane–AcOEt (5 : 1, v/v). The first eluate gave 218 mg (41.4%) of recovered starting material **2b**. The second eluate gave 190 mg of a mixture of **8** and **9**. This mixture was further subjected to preparative HPLC with hexane–AcOEt (5 : 1, v/v). The first eluate afforded 81 mg (15.0%) of 3β,28-diacetoxy-(20R)-lupan-29-al (**8**), colorless crystals (methanol–ether), mp 205—207 °C. The second eluate afforded 161.5 mg (29.8%) of 3β,28-diacetoxy-(20S)-lupan-29-al (**9**), colorless crystals (methanol–ether), mp 203—207 °C. Analysis by GLC-MS and GLC confirmed the formation of **2b** (rt, 19.45 min), **8** (rt, 28.76 min), and **9** (rt, 30.92 min). Yields are listed in Table 1. **8**: IR (KBr) cm^{-1}: 2952, 2868, 1726. ^{1}H-NMR (500 MHz, CDCl$_3$) δ: 0.84 (3H, m, C24-H), 0.85 (3H, s, C23-H), 0.86 (3H, s, C25-H), 0.95 (3H, s, C27-H), 1.05 (3H, s, C26-H), 1.10 (3H, d, J=7.02 Hz, C30-H), 1.10—1.98 (complex, CH$_2$ and CH), 1.71 (1H, m, C18-H), 2.05 (3H, s, OCOCH$_3$), 2.07 (3H, s, COCH$_3$), 2.57—2.65 (1H, m, C20-H), 3.79 (3H, d, J=11.29 Hz, C28-H), 4.21 (3H, d, J=11.29 Hz, C28-H), 4.48 (1H, dd, J=5.50, 9.77 Hz, C3α-H), 9.85 (3H, d, J=1.83 Hz, C29-H). $[\alpha]_D^{25}$ −15.76° (c=1.0, CHCl$_3$). MS m/z: 542 (M$^+$). HR-MS Calcd for $C_{34}H_{54}O_5$: 542.3971. Found: 542.3981. *Anal*. Calcd for $C_{34}H_{54}O_5$: C, 75.23; H, 10.03. Found: C, 75.25; H, 10.10. **9**: IR (KBr) cm^{-1}: 2944, 2870, 1730. ^{1}H-NMR (500 MHz, CDCl$_3$) δ: 0.84 (3H, s, C24-H), 0.85 (3H, s, C23-H), 0.87 (3H, s, C26-H), 0.96 (3H, s, C29-H), 0.97 (3H, s, C27-H), 1.04 (3H, d, J=7.02 Hz, C30-H), 1.06 (3H, s, C25-H), 1.10—1.95 (complex, CH$_2$ and C-H), 2.05 (3H, s, OCOCH$_3$), 2.07 (3H, s, COCH$_3$), 2.26—2.44 (1H, m, C19-H), 2.66 (1H, dq, J= 3.0, 7.0 Hz, C20-H), 3.75 (1H, J=11.29 Hz, C28-H), 4.21 (1H, J=11.29 Hz, C28-H), 4.40 (1H, dd, J=5.50, 10.68 Hz, C3α-H), 9.62 (1H, s, C29-H). $[\alpha]_D^{25}$ +10.57° (c=1.0, CHCl$_3$). MS m/z: 542 (M$^+$). HR-MS Calcd for $C_{34}H_{54}O_5$: 542.3971. Found: 542.3971. *Anal*. Calcd for $C_{34}H_{54}O_5$: C, 75.23; H, 10.03. Found: C, 75.21; H, 10.06.

Oxygenation of 2b with Reagent System B This reaction was carried out at room temperature for 2 h according to the procedure used for oxygenation of **1b** with reagent system B. The crude product was purified as the procedure described for the oxidation of **2b** with reagent system A to give **8**, **9**, and 20,29-epoxy-3,28-di-*O*-acetyl-betulin (**7**), colorless crystals (MeOH), mp 191—193 °C. Analysis by GLC-MS and GLC confirmed the formation of **8**, **9**, **7** (rt, 22.35 min), and **2b**. Yields are listed in Table 1.

Epoxidation of 1b with *m*-Chloroperoxybenzoic Acid To a stirred solution of **1b** (434 mg, 0.846 mmol) and 0.1 ml of saturated aqueous NaHCO$_3$ in CHCl$_3$ (8 ml) at 0 °C, *m*-chloroperbenzoic acid (299 mg, 1.73 mmol) was added in one portion, followed by stirring for 22 h. The resulting mixture was diluted with CH$_2$Cl$_2$ (200 ml), and washed with saturated NaHCO$_3$ and brine. After drying over Na$_2$SO$_4$, the solvent was evaporated and the residue was flash chromatographed over silica gel eluted with AcOEt–hexane (1 : 10, v/v) to afford 318 mg (71%) of methyl 3β-*O*-acetyl-12α,13α-epoxy-18β-oleanolate (**5**) as colorless powder, mp 195—197 °C.

$[\alpha]_D^{25}$ +21.44° (c=1.1, CHCl$_3$). This compound was used in rearrangement reactions without its recrystallization. IR (KBr) cm^{-1}: 2946, 2868, 1726, 1251. ^{1}H-NMR (500 MHz, CDCl$_3$) δ: 0.727 (1H, d, J=10.99 Hz, C5-H), 0.801 (3H, s, C30-H), 0.812 (3H, s, C26-H), 0.822 (3H, s, C24-H), 0.843 (3H, s, C23-H), 0.931 (3H, s, C29-H), 0.944 (3H, s, C25-H), 1.109 (3H, s, C27-H), 1.955 (1H, dd, J=4.24, 13.43 Hz, C16-H), 2.009 (1H, dd, J=4.28, 14.04 Hz, C18-H), 2.035 (3H, s, C3–OCOCH$_3$), 3.156 (1H, t, J= 1.83 Hz, C12-H), 3.683 (3H, s, –COOCH$_3$), 4.473 (1H, dd, J=5.49, 10.99 Hz, C3-H). MS m/z: 528 (M$^+$). *Anal*. Calcd for $C_{33}H_{52}O_5$: C, 74.96; H, 9.91. Found: C, 74.85; H, 9.80.

Epoxidation of 2b with *m*-Chloroperoxybenzoic Acid This reaction was carried out at room temperature for 2 h according to the procedure used for epoxidation of **1b** to give 20,29-epoxy-3,28-di-*O*-acetyl-betulin (**7**) in 85% yield, colorless crystal (MeOH), mp 191—193 °C. IR (KBr) cm^{-1}: 2944, 2868, 1739, 1389. ^{1}H-NMR (500 MHz, CDCl$_3$) δ: 0.84 (3H, s, C25-H), 0.85 (3H, s, C24-H), 0.86 (3H, s, C23-H), 0.97 (3H, s, C26-H), 0.84—1.66 (complex, CH$_2$ and CH), 1.03 (3H, s, C27-H), 1.25 (3H, s, C30-H), 2.05 (3H, s, OCOCH$_3$), 2.07 (3H, s, COCH$_3$), 2.59 (1H, d, J=4.58 Hz, C29-H), 2.66 (2H, d, J= 4.58 Hz, C29-H), 3.68 (1H, d, J=10.99 Hz, C28-H), 4.23 (3H, dd, J=1.22, 10.99 Hz, C28-H), 4.48 (1H, dd, J=5.49, 10.68 Hz, C3α-H). MS m/z: 542 (M$^+$). HR-MS Calcd for $C_{34}H_{54}O_5$: 542.3971. Found: 542.3982. *Anal*. Calcd for $C_{34}H_{54}O_5$: C, 75.23; H, 10.03. Found: C, 75.26; H, 10.08.

Procedure for Rearrangement of Epoxide 5 with Reagent System A A 30% aqueous H_2O_2 solution (0.03 ml, 0.3 mmol) was added dropwise to a vigorously stirred solution of **5** (52.8 mg, 0.1 mmol) and Fe(PA)$_3$ (21.1 mg, 0.05 mmol) in MeCN (7 ml) at room temperature and the reaction mixture was then stirred for 3 h. The reaction mixture was poured into ice water and extracted with ether. The organic layer was washed with saturated Na$_2$SO$_3$, NaHCO$_3$, and brine. The ethereal solution was dried and concentrated and the residue purified by column chromatography on silica gel with hexane–AcOEt (10 : 1, v/v) to give **6** and the recovered material **5**. Yields are listed in Table 2.

With Reagent System B A 30% aqueous H_2O_2 solution (0.03 ml, 0.3 mmol) was added dropwise to a solution of Fe(ClO$_4$)$_3$·9H$_2$O (25.8 mg, 0.05 mmol), picolinic acid (18.5 mg, 0.15 mmol), pyridine (19.8 mg, 0.25 mmol), and **5** (52.8 mg, 0.1 mmol) in MeCN (7 ml) and Ac_2O (0.1 ml) at room temperature with vigorous stirring, and the whole was stirred for 3 h. The reaction mixture was worked up according to the procedure described above. Analysis by GLC-MS and GLC confirmed the formation of **6** and the recovered material **5** (rt, 18.53). Yields are listed in Table 2.

With Fe(PA)$_3$ in MeCN Fe(PA)$_3$ (21.1 mg, 0.1 mmol) was added to a solution of **5** (52.8 mg, 0.1 mmol) in MeCN (7 ml) at room temperature and the reaction mixture was then stirred for 3 h. The reaction mixture was worked up according to the procedure described above. Analysis by GLC-MS and GLC confirmed the formation of **6** and the recovered material **5**. Yields are listed in Table 2.

With H$_2$O$_2$/Ac$_2$O in MeCN A 30% aqueous H_2O_2 solution (0.03 ml, 0.3 mmol) was added dropwise to a solution of **5** (52.8 mg, 0.1 mmol) in MeCN (7 ml) and Ac_2O (0.1 ml) at room temperature with vigorous stirring, and the whole was stirred for 3 h. The reaction mixture was worked up according to the procedure described above. Analysis by GLC-MS and GLC confirmed the formation of **6** and the recovered material **5**. Yields are listed in Table 2.

With Fe(ClO$_4$)$_3$·9H$_2$O in MeCN A solution of Fe(ClO$_4$)$_3$·9H$_2$O (25.8 mg, 0.05 mmol) and **5** (52.8 mg, 0.1 mmol) in MeCN (7 ml) was stirred for 3 h. The reaction mixture was worked up according to the procedure described above. Analysis by GLC-MS and GLC confirmed the formation of **6** along with another product. Yields are listed in Table 2.

Procedure for Rearrangement Reactions of Epoxide 7 with Reagent Systems A and B, and Fe(PA)$_3$ These reactions were carried out for 3 h by the procedure used for rearrangement of **5**. Analysis by GLC-MS and

GLC confirmed the formation of a mixture of **8** and **9**, and the recovered material **7**. Yields are listed in Table 2.

With $Fe(ClO_4)_3 \cdot 9H_2O$-PAH-Py in MeCN A solution of $Fe(ClO_4)_3 \cdot 9H_2O$ (25.8 mg, 0.05 mmol), picolinic acid (18.5 mg, 0.15 mmol), pyridine (19.8 mg, 0.25 mmol), and **5** (52.8 mg, 0.1 mmol) in MeCN (7 ml) was stirred for 3 h. The reaction mixture was worked up according to the procedure described above. Analysis by GLC-MS and GLC confirmed the formation of a mixture of **8** and **9**, and the recovered material **7**. Yields are listed in Table 2.

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