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# A novel allylic hydroxylation of sterically hindered olefins by Fe–porphyrin-catalyzed *m*CPBA oxidation

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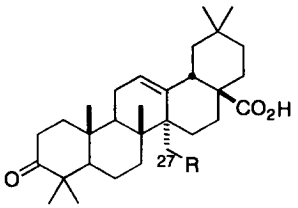
**Abstract**

A novel allylic hydroxylation by *m*CPBA of triterpenes bearing sterically hindered olefin is catalyzed by Fe(PFPP)Cl. Oleanolic acid, ursolic acid, dihydrolanosterol and their derivatives are converted to the corresponding allylic alcohols by *m*CPBA–Fe(PFPP)Cl under mild conditions. In contrast, for common or electron-deficient olefins, *m*CPBA–Fe(PFPP)Cl is an efficient epoxidation system. The intermediacy of an Fe–oxo-porphyrin and subsequent hydrogen abstraction and recombination are proposed for the selective α-hydroxylation of triterpenes.


We have reported on the novel triterpene endothelin receptor antagonist, myriceric acid A **1**, which is characterized by a 27-oxygenated oleanane skeleton.[1] For large-scale synthesis of **1**, we developed a semi-total synthesis of myricerone **2** starting from readily available oleanolic acid.[2] The method employing the Barton reaction to introduce a 27-hydroxy group offers a high yield, but required a number of steps. Direct hydroxylation of the 27-methyl group was thought to be an alternative short route to the 27-hydroxyoleanane triterpene. As cytochrome P-450 is a well-known enzyme for oxidizing the unreactive methyl group[3] and their model reaction was studied using a metal–porphyrin system,[4] we surveyed a variety of oxidation reactions including metal-catalyzed oxidation and microbial oxidation.




**1** : R = *O*-caffeoyl, myriceric acid A
**2** : R = OH, myricerone
**3** : R = H, 3-keto-oleanolic acid

To prepare myricerone **2**, we tried metal–porphyrin-catalyzed hydroxylation of 3-keto-oleanolic acid **3** using several commercially available metal–porphyrins, oxidants and solvents. No hydroxylation at the

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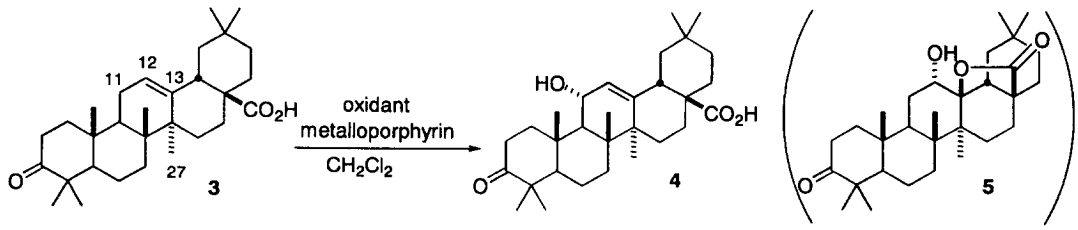
27-position was observed in any case. However a novel allylic hydroxylation of the 11-position was observed when we used *m*CPBA in combination with a catalytic amount of Fe(PFPP)Cl [PFPP=5,10,15,20-tetrakis(pentafluorophenyl)porphyrin].[5,6] In a typical run, **3** was treated with *m*CPBA (1.2 equiv.) in the presence of Fe(PFPP)Cl (3 mol%) at −78°C and 11α-hydroxy-3-keto-oleanolic acid **4** was obtained in 67% yield (Scheme 1).[7] No over-oxidation or side reaction such as 11-ketone formation, epoxidation or Bayer–Villiger oxidation was observed. The stereochemistry of the 11-α-hydroxy group of **4** was determined by comparison of the 11-β-hydroxy derivatives.[7] No allylic oxidation was observed without Fe(PFPP)Cl even with a large excess (4 equiv.) of *m*CPBA at a higher temperature (0°C), and hydroxylactone **5**, instead of 11-hydroxy-3-keto-oleanolic acid, was obtained in a low yield via epoxidation of the 12–13 double bond and subsequent lactonization.[2] Other porphyrins and oxidants were inactive (Table 1).



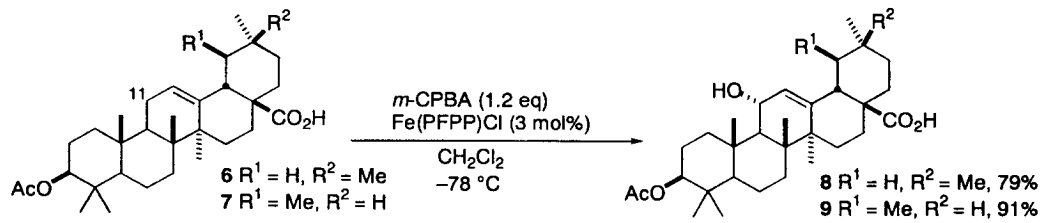

Scheme 1.

Table 1
Allylic hydroxylation of 3-keto-oleanic acid **3**

| entry | oxidant | metalloporphyrin | condition | product | yield |
|---|---|---|---|---|---|
| 1 | *m*-CPBA (1.2 eq.) | Fe(PFPP)Cl (3 mol%) | −78 °C, 4.5 h | **4** | 67% |
| 2 | *m*-CPBA (4.0 eq.) | none | 0 °C, 7.5 h | **5** | 33% |
| 3 | *m*-CPBA (1.2 eq.) | Fe(TPP)Cl (1 mol%) | 0 °C, overnight | no reaction | |
| 4 | $C_6H_5C(CH_3)_2OOH$ (2.5 eq.) N-methylimidazole (1.0 eq.) | Fe(PFPP)Cl (3 mol%) | −78 °C→0 °C | no reaction | |

PFPP = 5,10,15,20-tetrakis (pentafluorophenyl) porphyrin
TPP = 5,10,15,20-tetraphenylporphyrin

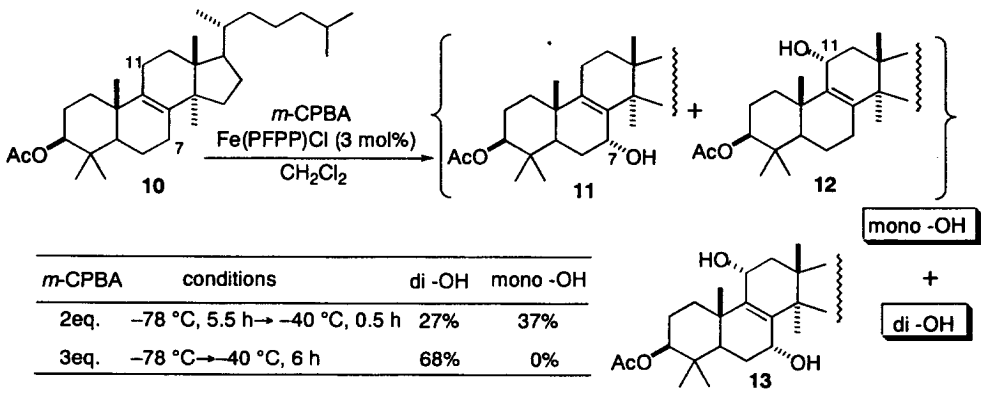
This allylic hydroxylation can be used in general for triterpenes having sterically hindered olefins, and oleanolic acid **6** and ursolic acid derivatives **7** gave the corresponding allylic alcohols **8**, **9** (Scheme 2) in moderate yields under the conditions employed for oxidation of **3**.




Scheme 2.

Dihydrolanosterol **10** underwent allylic hydroxylation at the 7- and 11-position non-selectively in the presence of 2 equiv. of *m*CPBA to give a mixture of allylic alcohols (**11**, **12**, **13**) (Scheme 3). However, the oxidation exploiting 3 equiv. of *m*CPBA led exclusively to allylic α-diol **13** in a high yield.[8] The stereochemistry of two α-hydroxy groups of **13** was determined by X-ray crystallography. The known 8–9 epoxide was obtained without the catalyst.[9] The novel allylic hydroxylation described above has

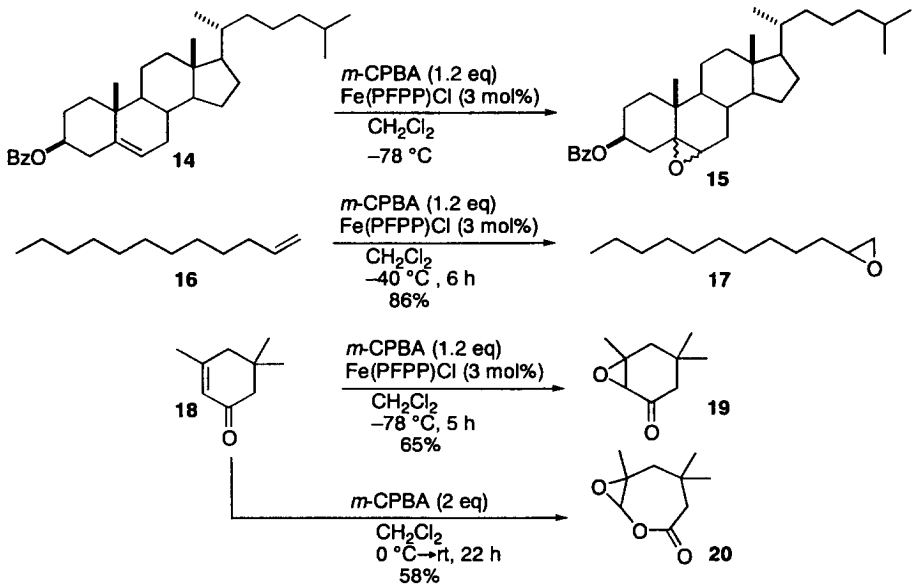
synthetic utility because allylic alcohols **8**, **13** had been prepared by a multi-step procedure and in a low yield.[8,10]




| *m*-CPBA | conditions | di -OH | mono -OH |
|---|---|---|---|
| 2eq. | –78 °C, 5.5 h→ –40 °C, 0.5 h | 27% | 37% |
| 3eq. | –78 °C→–40 °C, 6 h | 68% | 0% |

Scheme 3.

The allylic hydroxylation by *m*CPBA–Fe(PFPP)Cl was limited for the hindered olefins in triterpenes. For sterically unhindered olefins (**14**, **16**, **18**),[11,12] this oxidation system catalyzed an olefin epoxidation at a low temperature (Scheme 4). Even electron-deficient α,β-unsaturated ketone **18** gave epoxyketone **19** under mild conditions, and this is in contrast to the result of an experiment which was carried out without the catalyst giving epoxylactone **20** via the Bayer–Villiger reaction and a subsequent epoxidation.[12,13]




Scheme 4.

Mechanistically, the allylic hydroxylation is explained by analogy to that of the aldehyde oxidation to carboxylic acid by the same oxidation system.[6] Fe–oxo-porphyrin is envisioned to be initially formed from *m*CPBA and Fe(PFPP)Cl, and the putative oxo group is sterically hindered by a bulky porphyrin ring. This Fe–oxo-porphyrin complex was shown to be a highly potent epoxidation reagent for common unhindered olefins to give epoxides. However, access of the bulky Fe–oxo-porphyrin complex to the sterically hindered double bond of the triterpenes is prevented due to the steric hindrance between the bulky olefin and oxidant. Consequently, Fe–oxo-porphyrin complex abstracts an allylic hydrogen nearby

from the less hindered α-side to give a Fe–hydroxy-porphyrin complex and an allylic radical, which then recombine without loss of the arrangement of the two species[14,15] presumably within the solvent cage to yield the allylic α-alcohol regenerating the porphyrin catalyst.

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7. (a) Procedure for compound **4**. To a solution of **3** (115 mg, 0.33 mmol) and Fe(PFPP)Cl (11 mg, 3 mol%) in $CH_2Cl_2$ (6 mL) was added *m*CPBA (68 mg, 0.40 mmol) at −78°C, and the resulting mixture was stirred at the same temperature for 4 h. Saturated aqueous $NaHCO_3$ solution and saturated aqueous $Na_2S_2O_3$ solution were added to the mixture, and extracted twice with AcOEt. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography to give **4** (105 mg, 67%) as a colorless crystalline powder. Mp. 205–210°C (MeOH). (b) Microbial oxidation by of 3-ketooleanolic acid by *Marchantia polymorpha* HYA-1 and *Pyricularia apiculata* RF-168 gave both 11α-hydroxy- and 11β-hydroxy-3-keto-oleanolic acid, respectively (private communication from Dr. N. Shirane of Shionogi Research Laboratories). $^1$H NMR spectrum ($C_5D_5N$) of 11α-hydroxy-3-keto-oleanolic acid **4**: δ 0.91 (3H, s), 0.97 (3H, s), 1.08 (3H, s), 1.13 (3H, s), 1.18 (3H, s), 1.20 (3H, s), 1.39 (3H, s), 1.1–1.5 (14H, m), 1.7–2.2 (5H, m), 2.00 (H-9, 1H, d, *J*=8.8), 2.45–2.55 (1H, m), 2.61–2.72 (1H, m), 2.85–2.95 (1H, m), 3.36 (1H, dd, *J*=3.9, 13.7), 4.53 (H-11, 1H, dd, *J*=3.4, 8.8), 5.81 (1H, d, *J*=3.4). $^1$H NMR spectrum ($C_5D_5N$) of 11β-hydroxy-3-keto-oleanolic acid: δ 0.95 (3H, s), 0.99 (3H, s), 1.10 (3H, s), 1.20 (3H, s), 1.2–2.3 (19H, m), 1.25 (3H, s), 1.47 (3H, s), 1.71 (H-9, 1H, d, *J*=5.8), 1.79 (3H, s), 2.42–2.50 (1H, m), 2.61–2.68 (1H, m), 2.76–2.87 (1H, m), 3.41 (1H, dd, *J*=3.9, 13.7), 4.72 (H-11, 1H, dd, *J*=3.9, 5.8), 5.82 (1H, d, *J*=3.9). $^1$H NMR spectrum of compound **4** showed strong pseudo-*trans*-diaxal coupling constant between H-9 and H-11 (*J*=8.8) compared with the 11β-hydroxy derivative (*J*=5.8).
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