Ruthenium-Catalyzed Oxidative Transformation of Alkenes to α-Ketols with Peracetic Acid. Simple Synthesis of Cortisone Acetate

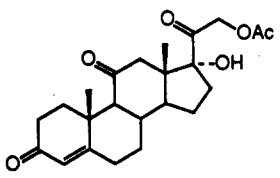
Shun-Ichi Murahashi,*,† Takao Saito,† Hidenori Hanaoka,† Yoshihide Murakami,† Takeshi Naota,† Hidenori Kumobayashi,‡ and Susumu Akutagawa‡

Department of Chemistry, Faculty of Engineering Science, Osaka University, Machikaneyama, Toyonaka, Osaka 560, Japan, and Takasago International Corporation, Kamata, Tokyo 144, Japan

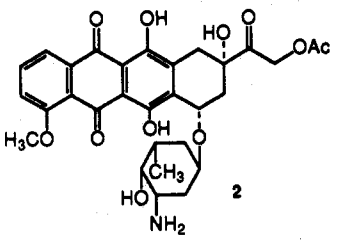
Received February 22, 1993

Summary: The reactions of alkenes with peracetic acid in the presence of $RuCl_3$ catalyst gave the corresponding α-ketols, which are important building units for synthesis of biological active compounds, such as cortisone acetate.

α-Ketols are important synthetic intermediates and partial structures of various biologically active compounds such as cortisone acetate (1)[1] and adriamycin acetate (2).[2]



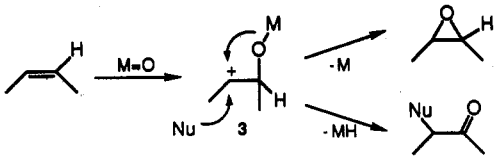
1



2

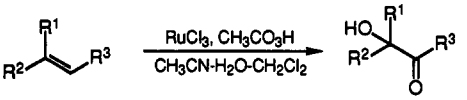
The methods for the synthesis of α-ketols from enol ethers[3] and enolates[4] have been studied extensively; however, those from olefins are limited to the oxidations with $KMnO_4$–$CuSO_4 \cdot 5H_2O$[5] and with isobutylaldehyde/O_2 in the presence of OsO_4 and bis(3-methyl-2,4-pentanedionato)nickel(II) catalysts.[6]

Recently, we found ruthenium-catalyzed oxidation of amines and amides with peroxides proceeds highly efficiently to give the corresponding α-oxygenated products.[7,8] In these reactions, nonporphyrin oxoruthenium species generated from low-valent ruthenium and peroxide undergoes cytochrome P-450-type reactions. One of the typical functions of cytochrome P-450 is epoxidation of alkenes, where cationic intermediate **3** has been postulated as a key intermediate (eq 1).[9] If one could trap the



(1)

intermediate **3** with nucleophiles such as water, a new type of catalytic oxidation of alkenes can be performed. Indeed, we found that novel oxidative transformation of olefins to α-ketols proceeds highly efficiently. Thus, the low-valent ruthenium-catalyzed oxidation of alkenes with peracetic acid in an aqueous solution under mild conditions gives the corresponding α-ketols (eq 2).[10]



(2)

Ruthenium trichloride has been found to be the best catalyst among those examined. The two-phase aqueous system is required for the present reaction. Without water, the cleavage of carbon–carbon bonds of alkenes occurs to give carboxylic acids predominantly. The oxidation is quite different from that promoted by ruthenium tetraoxide.[11] Indeed, the oxidation of 1-methylcyclohexene under the present reaction conditions gave 2-hydroxy-2-methylcyclohexanone (67%), while the oxidation of the same substrate under the conditions where ruthenium tetraoxide can be generated gave 6-oxoheptanoic acid (91%). Furthermore, the oxidation of diphenylacetylene gave benzil in 73% yield, while the similar oxidation with ruthenium tetraoxide gave benzoic acid.

The present oxidation can be applied to the oxidation of di- and trisubstituted alkenes generally. The representative results of the oxidation of alkenes are shown in Table I.[12] Acyclic and cyclic alkenes can be converted into the corresponding α-ketols in good yields. Small amount of byproducts, such as epoxides and 1,2-diols, can be removed readily by short chromatographic separation. Importantly, allylic acetates can be oxidized to give the corresponding acetoxy α-ketols in good to excellent yields. Particularly, the oxidation of 3-acetoxy-1-cyclohexene (**4**) gave (2*R**,3*S**)-3-acetoxy-2-hydroxycyclohexanone (**5**) chemo- and stereoselectively. Similarly, the oxidation of

† Osaka University.

‡ Takasago International Corporation.

(1) Fieser, L. F.; Fieser, M. In *Steroids*: Reinhold Publishing: New York, 1959; p 600. *Natural Products Chemistry*; Nakanishi, K., Goto, T., Ito, S., Natori, S., Nozoe, S., Eds.; Kodansha/Academic Press: New York, 1974; Vol. 1, p 421.

(2) Arcamone, F. *Top. Antibiot. Chem.* **1978**, *2*, 102.

(3) Hashiyama, T.; Morikawa, K.; Sharpless, K. B. *J. Org. Chem.* **1992**, *57*, 5067 and references cited therein.

(4) Davis, F. A.; Sheppard, A. C.; Chen, B.-C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679 and references cited therein.

(5) Baskaran, S.; Das, J.; Chandrasekaran, S. *J. Org. Chem.* **1989**, *54*, 5182.

(6) Takai, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1991**, 1499.

(7) Murahashi, S.-I. *Pure Appl. Chem.* **1992**, *64*, 403.

(8) Amines: (a) Murahashi, S.-I.; Naota, T.; Taki, H. *J. Chem. Soc., Chem. Commun.* **1985**, 613. (b) Murahashi, S.-I.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* **1988**, *110*, 8256. (c) Murahashi, S.-I.; Naota, T.; Miyaguchi, N.; Nakato, T. *Tetrahedron Lett.* **1992**, *33*, 6991. Amides: (d) Murahashi, S.-I.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* **1990**, *112*, 7820.

(9) (a) Ostovic, D.; Bruice, T. C. *J. Am. Chem. Soc.* **1989**, *111*, 6511. (b) Castellino, A. J.; Bruice, T. C. *Ibid.* **1988**, *110*, 158, 7512. (c) Traylor, T. G.; Xu, F. *Ibid.* **1988**, *110*, 1953. (d) Traylor, T. G.; Miksztal, A. R. *Ibid.* **1987**, *109*, 2770.

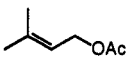
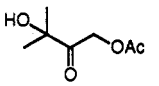
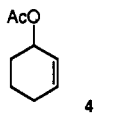
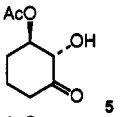
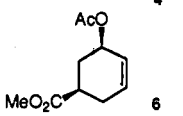
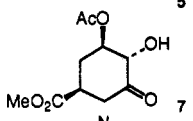
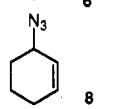
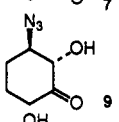
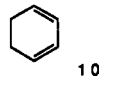
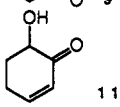
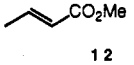
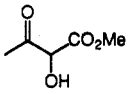
(10) Presented at the 61st Annual Meetings of the Chemical Society of Japan (Tokyo), 1991, Abstracts 1C918 and 1C925. See also ref 6.

(11) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936 and references cited therein.

(12) Typical procedure is as follows. To a stirred mixture of **4** (0.701 g, 5.00 mmol), $RuCl_3 \cdot 3H_2O$ (0.039 g, 0.15 mmol), dichloromethane (5.0 mL), acetonitrile (5.0 mL), and water (5.0 mL) was added a 30% solution of peracetic acid in ethyl acetate (3.8 g, 15 mmol) dropwise at room temperature over a period of 2 h, and the mixture was stirred for additional 3 h. Then, the reaction mixture was poured into a 5% Na_2SO_3 solution in water and extracted with dichloromethane (25 mL × 5). The combined extracts were washed with brine (50 mL) and dried over $MgSO_4$. Removal of the solvent followed by short column chromatography on SiO_2 (hexane/ethyl acetate = 1/1) gave **5** (0.603 g, 70%).

0022-3263/93/1958-2929$04.00/0

Table I. Ruthenium-Catalyzed Oxidative Transformation of Alkenes to α-Ketols with Peracetic Acid

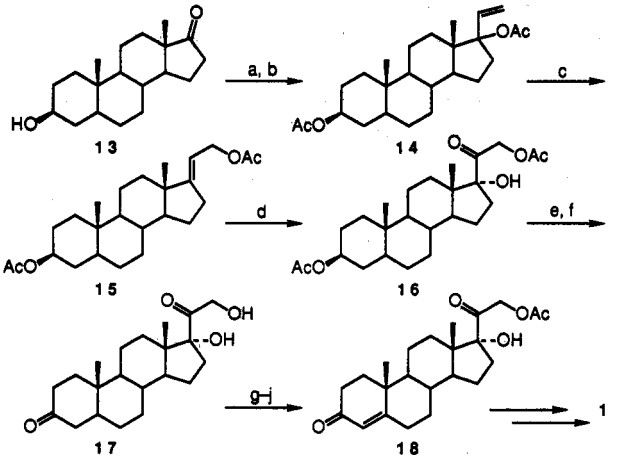
entry	substrate	product[a]	yield,[b] %
1			78
2	 4	 5	70[c]
3	 6	 7	55[c]
4	 8	 9	65[c]
5	 10	 11	41
6	 12		56

[a] The product gives satisfactory IR, NMR, and mass spectral data and analysis. [b] Isolated yield based on the starting olefin. [c] Single diastereomer.

cis-5-(methoxycarbonyl)-2-cyclohexenyl acetate (**6**) gave (2*R**,3*S**,5*R**)-3-acetoxy-2-hydroxy-5-(methoxycarbonyl)-1-cyclohexanone (**7**) selectively. The oxidation of allyl azide **8** also proceeds chemo- and stereoselectively to give (2*R**,3*S**)-3-azido-2-hydroxycyclohexanone (**9**). These reactions are highly useful for synthesis of sugars and aminosugars. The oxidation of 1,3-cyclohexadiene (**10**) proceeds to give the α-ketol **11** regioselectively. The oxidation of α,β-unsaturated carbonyl compounds such as methyl crotonate (**12**) gave the corresponding α-ketols, indicating that direct oxidation with peracetic acid is not involved in these reactions.[13]

The efficiency of the present reaction has been demonstrated by the synthesis of cortisone acetate (**1**),[14] which is a valuable antiinflammatory agent. Our strategy for the synthesis of **1** is shown in Scheme I. Epiandrosterone (**13**), which is commercially available, was converted into 3β,17ξ-diacetoxy-5α-pregn-20-ene (**14**) (mp 152–153.5 °C) upon treatment with vinylmagnesium bromide followed by (*N*,*N*-dimethylamino)pyridine and Ac_2O in dry pyridine. Catalytic rearrangement of **14** with $PdCl_2(CH_3CN)_2$ catalyst[15] in THF at room temperature gave 3β,21-diacetoxy-5α-pregn-17-ene (**15**) (mp 153–154.5 °C) in 92% yield. The present ruthenium-catalyzed oxidation of **15** proceeds stereoselectively to give 20-oxo-5α-pregnane-3β,-17α,21-triol 3,21-acetate (**16**) (mp 202–203.5 °C, $[\alpha]_D$ +28.0° (*c* 1.03, $CHCl_3$)) in 57% yield. Hydrolysis of **16** followed by oxidation with *N*-bromoacetamide gave **17**.

Scheme I [a]



[a] Key: (a) CH_2=$CHMgBr$; (b) Ac_2O, DMAP/pyridine; (c) $PdCl_2(CH_3CN)_2$ (cat.); (d) $RuCl_3$ (cat.), CH_3CO_3H; (e) KOH; (f) NBA; (g) Ac_2O; (h) Br_2; (i) 2,4-$(NO_2)_2C_6H_3NHNH_2$; (j) CH_3COCO_2H.

Acetylation followed by dehydrogenation gave **18** (mp 235–236 °C, $[\alpha]_D$ +114° (*c* 0.245, acetone)),[16] which can be converted into **1** by microbial oxidation with *Rhizopus nigricans*.[17]

The reaction can be rationalized by assuming three pathways which involve direct formation of α-ketols from alkenes (path A), formation of epoxides followed by ring opening (path B), and formation of 1,2-diols and subsequent oxidation (path C). The following control experiments for the oxidation of 5-decene exclude path B and path C: (i) The oxidation of 5,6-decanediol under the reaction conditions gave 5,6-decanedione and pentanoic acid rather than the corresponding α-ketol. (ii) *cis*- and *trans*-5,6-epoxydecanes were recovered completely under the reaction conditions. Although it is premature to discuss the mechanism at the present stage, the reaction can be rationalized by assuming the following reaction pathways: The reaction of the Ru(III) complex with peracetic acid would give Ru(V)=O species,[8] which undergoes reaction with olefins to give cationic species **3**. Nucleophilic attack of water before ring closure to give epoxide[18] and subsequent β-elimination of ruthenium hydride species would give α-ketols. Actually, the oxidation of 2,3-dimethyl-2-butene which has no β-hydrogen atom gave 2,3-dihydroxy-2,3-dimethylbutane exclusively.

Work is in progress to provide definitive mechanistic information and to apply our method to other systems.

Supplementary Material Available: Experimental procedures and spectral data for all compounds (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(13) The oxidation of **12** with peracetic acid in the absence of the catalyst does not occur under the similar reaction conditions.

(14) Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1989**, *111*, 6257 and references cited therein.

(15) (a) Overman, L. E.; Knoll, F. M. *Tetrahedron Lett.* **1979**, *4*, 321. (b) Grieco, P. A.; Takigawa, T.; Bongers, S. L.; Tanaka, H. *J. Am. Chem. Soc.* **1980**, *102*, 7587.

(16) Julian, P. L.; Meyer, E. W.; Karpel, W. J., Waller, I. R. *J. Am. Chem. Soc.* **1950**, *72*, 5145.

(17) Peterson, D. H.; Eppstein, S. H.; Meister, P. D.; Magerlein, B. J.; Murray, H. C.; Leigh, H. M.; Weintraub, A.; Reineke, L. M. *J. Am. Chem. Soc.* **1953**, *75*, 412.

(18) The oxidation of *cis*-5-decene gave 6-hydroxy-5-decanone (30%) along with *trans*-5,6-epoxydecane (5%) and *cis*-5,6-epoxydecane (15%), suggesting the presence of intermediate **3** in this oxidation reaction.