Pergamon

Tetrahedron Letters, Vol. 36, No. 11, pp. 1879-1882, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00173-5

γ-Selective Hydroxylation of α,β,γ,δ-Unsaturated Carbonyl Compounds and Its Application to Syntheses of (±)-6-Hydroxyshogaol and Related Furanoids

Yoh-ichi MATSUSHITA* , Kazuhiro SUGAMOTO, Tuyoshi NAKAMA, Toshifumi SAKAMOTO, and Takanao MATSUI

Faculty of Engineering, Miyazaki University, Gakuen-Kibanadai, Miyazaki 889-21, JAPAN

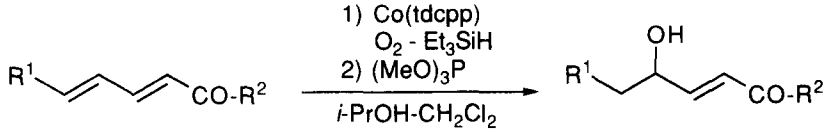
Mitsuru NAKAYAMA

College of Agriculture, University of Osaka Prefecture, Gakuen-cho, Sakai 593, JAPAN

Abstract: α,β,γ,δ-Unsaturated carbonyl compounds were converted regioselectively into γ-hydroxy-α,β-unsaturated carbonyl compounds by reduction-oxygenation with molecular oxygen and triethylsilane in the presence of cobalt(II) porphyrin as a catalyst followed by treatment with trimethyl phosphite. (±)-6-Hydroxyshogaol and related furanoids isolated from ginger were synthesized *via* this method.

γ-Hydroxy-α,β-unsaturated carbonyl compounds are important features of many natural products having biological activities such as palulolide C,[1] brefeldin A,[2] and 6-hydroxyshogaol.[3] In a variety of their synthetic methods, Wittig olefination of α-hydroxy aldehydes and ketones[4] and allylic oxidation of α,β-unsaturated esters with selenium dioxide[5] have been used commonly. We have previously reported that cobalt(II) porphyrin-catalyzed reduction-oxygenation of α,β,γ,δ-unsaturated esters followed by treatment with acetic anhydride and 4-(*N*,*N*-dimethylamino)pyridine gave the corresponding γ-oxo compounds,[6] and the synthesis of (-)-pyrenophorin was achieved by the application of this method.[7] In addition, benzyl alcohols and α-hydroxyalkanoic esters were found to be produced from styrenes and acrylic esters, respectively, by the reduction-oxygenation followed by reducing the intermediary hydroperoxides with trimethylposphite.[8] In the connection with our oxygenation method, we will discribe herein a regioselective hydroxylation of α,β,γ,δ-unsaturated carbonyl compounds to γ-hydroxy-α,β-unsaturated carbonyl compounds by the cobalt(II) porphyrin-catalyzed oxygenation and then *in situ* reduction with trimethyl phosphite, and syntheses of (±)-6-hydroxyshogaol and its related furanoids *via* this method.

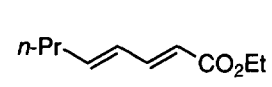
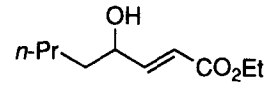
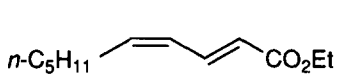
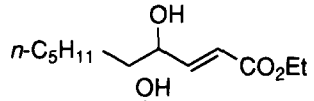
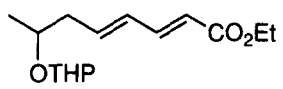
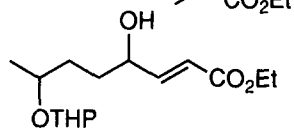
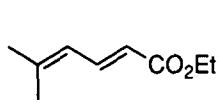
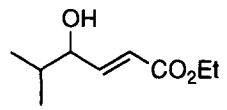
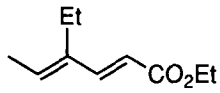
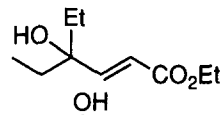
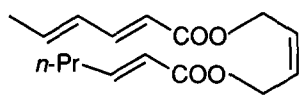
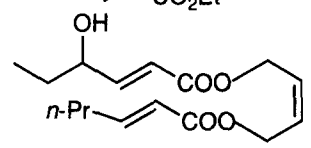
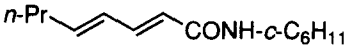
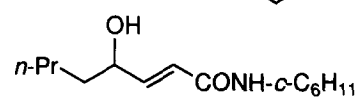
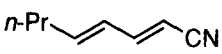
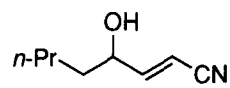
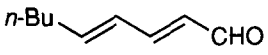
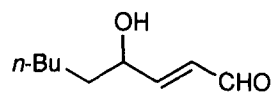
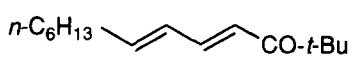
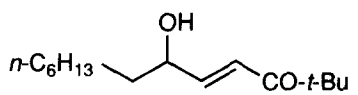
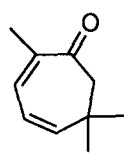
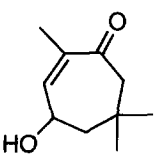
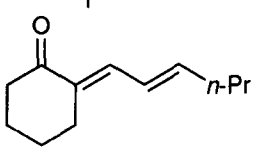
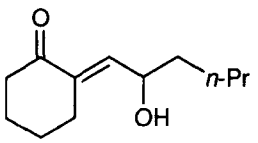
The potential of selective hydroxylation of α,β,γ,δ-unsaturated carbonyl compounds was initially examined (Scheme 1): α,β,γ,δ-unsaturated carbonyl compound (1 mmol) was allowed to react with oxygen (1 atm) and triethylsilane (1.2 eq.) in the presence of [5,10,15,20-tetrakis(2,6-dichlorophenyl)porphinato]cobalt(II)



R^1 = Alkyl, R^2 = H, Alkyl, OR, or N(R)R'

Scheme 1.

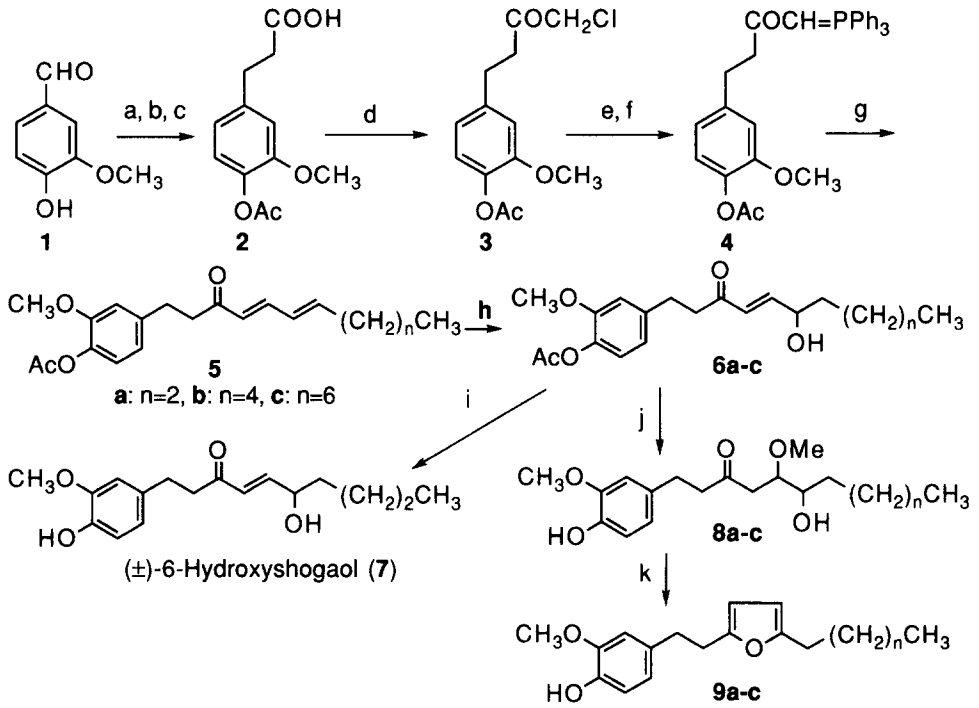
Table 1. The Hydroxylation of α,β,γ,δ-Unsaturated Carbonyl Compounds.

Entry	Substrate	Product	Time/h[a]	Yield/%[b]
1			1	82
2			1	79
3			1	87
4			2	81
5			2	87
6			3	71
7			2	70
8			2	71[d]
9			1.5	54
10			0.5	73
11			0.5	70
12			1	59

a) Reaction time for the reduction-oxygenation step. b) Isolated yield. c) The mixture of geometrical isomers was employed; 2*E*,4*E* / 2*Z*, 4*E* = 3/1. d) Total yield of isomers; 2*E* / 2*Z* = 7/2 determined by ^{1}H-NMR.

(Co(tdcpp)) (0.001 eq.) in 2-propanol-dichloromethane (5 ml- 5 ml) at 28°C until consuming the substrate completely by checking with tlc, followed by treatment with trimethyl phosphite (1.3 eq.) for 2h at room temperature. The results were summarized in Table 1. The dienoic esters, amides, and nitrile were converted to the corresponding γ-hydroxy-α,β-unsaturated compounds in good yields (Entries 1-8). Similarly good yields and reactivities were observed irrespective of configuration of the double bond on γ,δ-position (Entries 1 and 2). The alkyl substituents on the dienoyl group had no influence on the product yields (Entries 4 and 5). The selective reaction of dienoyl moiety of the substrate was capable even in the presence of other types of olefin moieties (Entries 6). The dienal and both acyclic and cyclic dienones were also hydroxylated smoothly (Entries 9-12). It is noteworthy that functional groups sensitive to acid or reduction such as terahydropyranyl (THP) ether, aldehyde, and ketone were remained under the reaction conditions. In all cases, the hydroxylation proceeded predominantly at γ-position of α,β,γ,δ-unsaturated carbonyl compounds. The products were obtained as a racemate.

Having developed a new method for the preparation of γ-hydroxy-α,β-unsaturated carbonyl compounds, we then investigated syntheses of (±)-6-hydroxyshogaol and the related furanoids, new antioxidative compounds isolated from ginger (Scheme 2).[9] Vanillin (**1**) was successively subjected to acetylation, the Knoevenagel condensation with malonic acid, hydrogenation, to give 3-(4-acetoxy-3-methoxyphenyl)propanoic acid (**2**) in 53% yield: Mp. 103.0-104.0°C (*n*-Hexane-EtOAc). Treatment of **2** with thionyl chloride, diazomethane and then



(a) Ac_2O (2.0 eq.), Py, CH_2Cl_2 , rt, 21 h, 98%; (b) $CH_2(COOH)_2$ (2.0 eq.), piperidine (0.15 eq.), Py, rt, 1 week, 61%; (c) H_2 (1 atm), 10% Pd-C, EtOAc, rt, 2 d, 88%; (d) $SOCl_2$ (1.5 eq.), cat. DMF, benzene, rt, 24 h; excess CH_2N_2 , Et_2O; excess HCl, CH_2Cl_2 , 0°C, 93% (3 steps); (e) Ph_3P (1.0 eq.), benzene, 60°C, 3 d, 98%; (f) 2 mol/*l* NaOH (1 eq.), dioxane, 0°C, rt, 98%; (g) $CH_3(CH_2)_nCH$=CH-CHO (2 eq.), benzene, reflux, 20~44 h, 81% (n=2), 89% (n=4), and 81% (n=6); **(h) Co(tdcpp) (0.001 eq.), O_2 (1 atm), Et_3SiH (1.2 eq.), *i*-PrOH-CH_2Cl_2 , rt, 1 h; then $(CH_3O)_3P$ (1.2 eq.), rt, 2 h, 80% (n=2), 66% (n=4), and 64% (n=6)**; (i) $Me_2NCH_2CON(Me)OH$ (2.0 eq.), THF- Phosphate buffer (pH 7.6), 50°C, 43 h, 50% (n=2); (j) 1 mol/*l* NaOH, MeOH, rt, 12 h, quant.; (k) SiO_2 , benzene, reflux, 5 h, 65% (n=2), 55% (n=4), and 70% (n=6)

Scheme 2.

hydrogen chloride gave the chloromethyl ketone **3** in 93% yield, which was allowed to react with triphenylphosphine followed by treating with 2 mol/*l* NaOH, to afford the ylid **4** in 96% yield. The Wittig reaction of (2*E*)-alkenals with **4** in refluxing benzene yielded the dienones **5a-c** in high yields. The dienones **5a-c** were hydroxylated by the Co(tdcpp)-catalyzed reduction-oxygenation followed by treatment with trimethyl posphite under the same conditions as descibed above, to give the hydroxyketone **6a-c** in good yields. (±)-6-hydroxyshogaol (**7**) was synthesized in 50% yield (total yield from **1**: 15%) by neutral hydrolysis of **6a** using *N*-methyl-2-dimethylaminoacetohydroxamic acid[10] in THF- 0.1 mol/*l* phosphate buffer (pH 7.6) at 50°C; some attempts of basic hydrolysis of **6a** using aqueous alkaline solution were failed. On the other hand, hydrolysis of **6a-c** with 1 mol/*l* NaOH in methanol gave crude methanol-adducts **8a-c**, which were subsequently treated with silica-gel in refluxing benzene, yielding the natural furanoids **9a-c** in 20%, 15%, and 17% yield from **1**, respectively. The IR and ^{1}H- and ^{13}C-NMR spectral data of synthesized **7** and **9a-c** were coincided with those of the natural ones.[3, 11]

Thus the cobalt porphyrin-catalyzed reduction-oxygenation of α,β,γ,δ-unsaturated carbonyl compounds followed by reduction with trimethyl phosphite provides a chemo- and regioselective method for synthesis of γ-hydroxy-α,β-unsaturated carbonyl compounds and total syntheses of (±)-6-hydroxyshogaol and the related furanoids were achived by the application of the present method.

The authors are grateful to Professor N. Nakatani of Faculty of Science of Living, Osaka City University, Japan, for the spectral confirmation of synthetic products coincident with natural ones. This work was partially supported by a Grant-in-Aid for Scientific Research form the Ministry of Education, Science and Culture of Japan, and by a Reseach Grant from the Asahi Glass Foundation in Japan.

References and Notes

1 D. Rodphaya, J. Sekiguchi, and Y. Yamada, *J. Antibiotics*, **1986**, 39, 629-635.
2 H. P. Weber, D. Hauser, and H. P. Sigg, *Helv. Chim. Acta*, **1971**, 54, 2763-2766.
3 N. Nakatani and H. Kikuzaki, *Chemistry Express*, **1992**, 7, 221-224.
4 P. Garner and S. Ramakanth, *J. Org. Chem.*, **1987**, 52, 2629-2631, and references therein.
5 H. J. Bestmann and R. Schobert, *Angew. Chem. Int. Ed. Engl.*, 1985, 24, 791-792.
6 Y. Matsushita, K. Sugamoto, and T. Matsui, *Chem. Lett.*, **1992**, 2165-2168.
7 Y. Matsushita, H. Furusawa, T. Matsui, and M. Nakayama, *Chem. Lett.*, **1994**, 1083-1084.
8 Y. Matsushita, K. Sugamoto, and T. Matsui, *Chem. Lett.*, **1993**, 925-928.
9 Selective data for synthetic compounds. **3**: Mp. 63.0-63.5°C (*n*-Hexane-EtOAc); IR ($CHCl_3$) 1780 and 1740 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) δppm 2.30 (3H, s, -OCOC$\underline{H}_3$), 2.93 (4H, s, -(C$\underline{H}_2$)$_2$-), 3.82(3H, s, -OC$\underline{H}_3$), 4.04 (2H, s, -C$\underline{H}_2$Cl), 6.7-7.0 (3H, m, aromatic protons). **4**: Mp. 128.0-129.0°C (*n*-Hexane-EtOAc), IR ($CHCl_3$) 1770, 1750(sh) cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) δppm 2.30 (3H, s, -OCOC$\underline{H}_3$), 2.4-3.2 (4H, m, -(C$\underline{H}_2$)$_2$-), 3.78 (3H, s, -OC$\underline{H}_3$), 6.7-7.0 (3H, m, aromatic protons), 7.4-7.8 (16H, m, -C$_6\underline{H}_5$ and -C$\underline{H}$=PPh$_3$). **5a**: colorless oil; IR ($CHCl_3$) 1780, 1690, 1670, 1650, 1610 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) δppm 0.92 (3H, t, J= 6.5 Hz, -C$\underline{H}_3$), 1.2-1.7 (2H, m, -C$\underline{H}_2$CH$_3$), 2.0-2.2.3 (2H, m, -C$\underline{H}_2$-C$_2$H$_5$), 2.29 (3H, s, -OCOC$\underline{H}_3$), 2.90 (4H, s, -(C$\underline{H}_2$)$_2$-Ar), 3.80 (3H, s, -OC$\underline{H}_3$), 5.94-6.25 (3H, m, olefinic protons), 6.7-7.3 (4H, m, aromatic protons and olefinic proton). **6a**: colorless oil; IR ($CHCl_3$) 3650, 1780, 1700, 1620 cm^{-1}; ^{1}H-NMR (60 MHz, $CDCl_3$) δppm 0.90 (3H, t, J= 6.5 Hz, -C$\underline{H}_3$), 1.1-1.8 (6H, m, -(C$\underline{H}_2$)$_3$-CH$_3$), 2.06 (1H, brs, -O$\underline{H}$), 2.29 (3H,s, -OCOC$\underline{H}_3$), 2.90 (4H, s, -(C$\underline{H}_2$)$_2$-Ar), 3.80 (3H, s, -OC$\underline{H}_3$), 4.30 (1H, m, -C$\underline{H}$(OH)-), 6.23 (1H, d, J= 15.8 Hz, -CO-C$\underline{H}$=), 6.60-7.05 (4H, m, aromatic protons and -CO-CH=C$\underline{H}$-).
10 M. Ono and I. Itoh,*Tetrahedron Lett.*, **1989**, 30, 207-210.
11 The stereochemical configuration of natural 6-hydroxyshogaol has not been determined.

(*Received in Japan* 29 *November* 1994; *revised* 11 *January* 1995; *accepted* 19 *January* 1995)