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An Efficient Method for Selective Acetylation of Alcoholic Hydroxyl Groups

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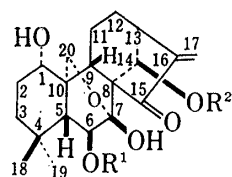
Acetylation of the C-6 hydroxyl group in oridonin (**1**), which is difficult by the use of acetic anhydride in pyridine, was investigated using acetic anhydride in the presence of some Lewis acids. A reagent system of acetic anhydride in the presence of a catalytic amount of boron trifluoride etherate was shown to be effective for this purpose. This reagent system was shown to be useful for selective acetylation of the alcoholic group(s) in compounds which have both alcoholic and phenolic hydroxyl groups.

Keywords—oridonin; chemoselective acetylation; hydrogen-bonding; alcoholic hydroxyl group; Lewis acid; exhaustive acetylation; diterpene

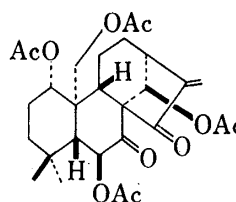
Acylation of the hydroxyl group has been used as an important protecting method. Recently it was reported that the antitumor activity of tumor inhibitors having hydroxyl group(s) is often enhanced by acylation of the hydroxyl group(s).¹⁾ Hence, we have been interested in the development of new or improved acylating methods for the hydroxyl or amino group as a part of our studies on antitumor compounds.^{2,3)}

We wish to reported here a reagent system, (RCO)₂O-catalytic BF₃·Et₂O, that is useful for selective acylation of the C-6 hydroxyl group in the oridonin molecule (**1**) and also for the chemoselective acetylation of alcoholic hydroxyl group(s) of compounds which possess both phenolic and alcoholic groups.

We previously suggested that hydrogen-bonding between the C-6 hydroxyl group and the C-15 carbonyl group in oridonin (**1**) may be an important factor in the antitumor activity.⁴⁾



- 1** : R¹=R²=H
2 : R¹=Ac, R²=H
3 : R¹=R²=Ac



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In order to validate this hypothesis, we planned to investigate the antitumor activity of C-6 acyloxyl derivatives which have no such hydrogen-bonding. On acetylation with acetic anhydride in pyridine, oridonin afforded the undesired 1,14-diacetate **5**.⁵⁾ On treatment with acyl chloride and triethylamine, oridonin gave only the 14-O-acyl derivative **7**.⁶⁾ (Chart 1).

Thus, we attempted the acetylation of oridonin (**1**) with excess acetic anhydride in the presence of a Lewis acid [TiBr₃·4H₂O, AlCl₃, BF₃·Et₂O, ZnCl₂, or Cu(ClO₄)₂·6H₂O] in tetrahydrofuran (THF). The use of TiBr₃·4H₂O, AlCl₃, and BF₃·Et₂O resulted in the formation of the 6,14-diacetate **3** as the major product (see Table I).

It is especially notable that oridonin (**1**) on treatment with excess Ac₂O and a catalytic amount of BF₃·Et₂O under ice-cooling gave the desired C-6 acetate **2** in 25.1% yield.⁸⁾ On

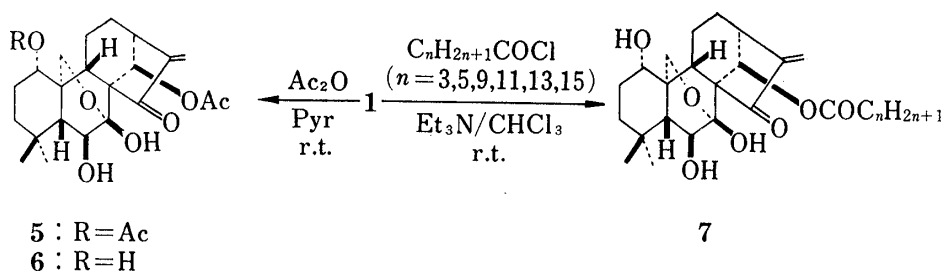


Chart 1

TABLE I. Acetylation of Oridonin (1) with Ac_2O -Lewis Acid

Lewis acid	Reaction conditions ^{a)}		Yield (%) ^{c)} of acetate		
	Temp ^{b)}	Time	Mono-acetate 2	Di-acetate 3	Tetra-acetate 4 ⁷⁾
$\text{TiBr}_3 \cdot 4\text{H}_2\text{O}^{d)}$	I	15 min		91.0	
$\text{AlCl}_3^{d)}$	r.t.	2 h		33.3	11.6
$\text{BF}_3 \cdot \text{Et}_2\text{O}^{e)}$	I	1 h	25.1	63.8	
$\text{ZnCl}_2^{d)}$	I	30 min		51.5% recovery of 1	
$\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}^{d)}$	I	30 min		51.0% recovery of 1	

a) The reaction was carried out in THF using excess Ac_2O .

b) I: ice-cooling. r.t.: room temperature.

c) Isolated yield.

d) 5 mol. equiv. of Lewis acid was used.

e) 0.23 mol. equiv. of Lewis acid was used.

treatment with the more bulky dodecanoic anhydride in the presence of a catalytic amount of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ at room temperature, oridonin (1) afforded only the 6-dodecanoate **8** in 83% yield. On the other hand, oridonin (1) on treatment with the same anhydride in pyridine gave the 14-dodecanoate **9** as a sole product (Chart 2). The structure assignment of the *O*-acyl derivatives was based on their ^1H -NMR and ^{13}C -NMR spectra.⁶⁾

The selective acylation at the C-6 hydroxyl group may be explicable as follows. In this reagent system, acid anhydride may be activated to an active species **10**, which must

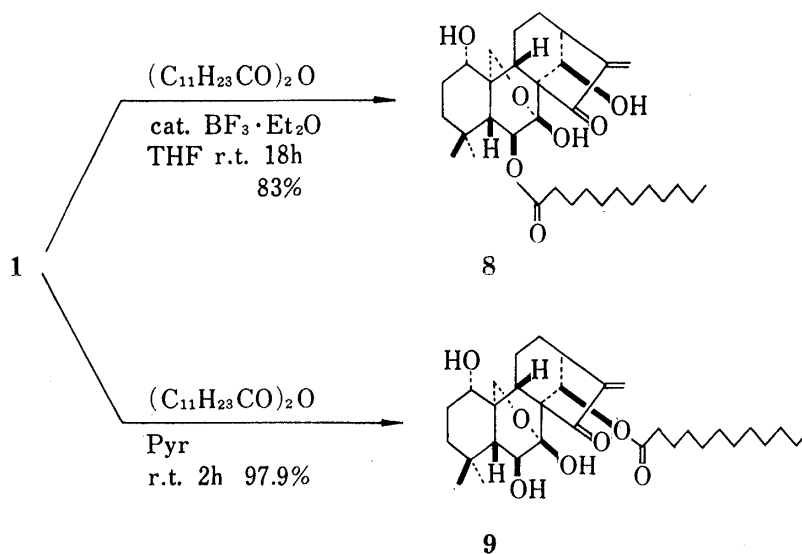
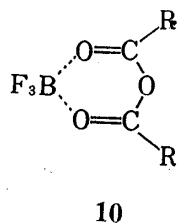


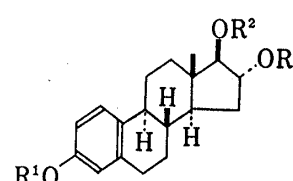
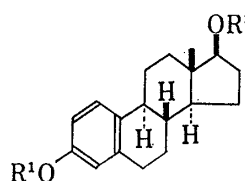
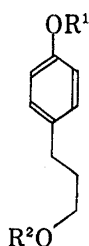
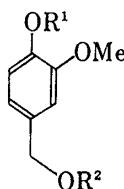
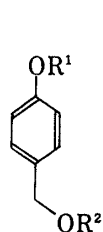
Chart 2

acylate the hydroxyl group having the stronger nucleophilicity more easily. The oxygen atom of the C-6 hydroxyl group has the strongest nucleophilicity because of the hydrogen-bonding with the C-15 carbonyl group.



If this explanation is correct, selective acetylation of the alcoholic hydroxyl group in a compound which has both alcoholic and phenolic hydroxyl groups should be possible with this reagent system.

Thus we attempted the selective acetylation of the diols **11**, **14**, **17**, **20** and estra-1,3,5(10)-triene-3,16 α ,17 β -triol(3,16 α ,17 β -estriol) (**24**) with an excess of Ac₂O and a catalytic amount of BF₃·Et₂O under ice-cooling or at room temperature. In all cases, selective acetylation of the alcoholic hydroxyl group(s) was achieved as expected. The results are summarized in Table II.



11: R¹=R²=H **14**: R¹=R²=H **17**: R¹=R²=H
12: R¹=H, **15**: R¹=H, **18**: R¹=H,
 R²=Ac R²=Ac R²=Ac
13: R¹=R²=Ac **16**: R¹=R²=Ac **19**: R¹=R²=Ac

20: R¹=R²=H
21: R¹=H, R²=Ac
22: R¹=R²=Ac
23: R¹=Ac, R²=H

24: R¹=R²=H
25: R¹=H, R²=Ac
26: R¹=R²=Ac

TABLE II. Acetylation of Some Compounds having Both Alcoholic and Phenolic Hydroxyl Group(s)

Substrate	Reaction conditions ^{a)}			Yield (%) of acetate
11	A	r.t.	4 ^{b)}	12 (68.0)
11	B	r.t.	3.5	13 (62.0)
14	A	r.t.	1.5	15 (54.9)
14	B	r.t.	16.5	16 (74.0)
17	A	I	1	18 (78.4), 19 (15.9)
17	B	r.t.	4	19 (92.1)
20	A	I	4.5	21 (61.1)
20	B	r.t.	17	22 (73.1)
20	B	I	1	22 (3.4), 23 (63.1)
24	A	r.t.	0.3	25 (100)
24	B	r.t.	24	26 (93.2)

a) A: The substrate was treated with Ac₂O and a catalytic amount of BF₃·Et₂O in THF.
 B: The substrate was treated with Ac₂O in pyridine. r.t.: at room temperature. I: under ice-cooling.

b) reaction time: h.

Selective acetylation of the phenolic hydroxyl group of these diols and triol with Ac₂O in pyridine was not successful except in the case of estra-1,3,5(10)-triene-3,17 β -diol(3,17 β -estradiol) (**20**). The Ac₂O-pyridine system is generally suitable for exhaustive acetylation under mild conditions (see Table II). Recently Mukaiyama and coworkers⁹⁾ reported a new reagent system for selective acetylation of the phenolic hydroxyl group; they acetylated 4-hydroxymethylphenol (**11**) to phenol acetate **27** in 71% yield (see Chart 3).

Thus our reagent system and their system are complementary to each other, and should be of great synthetic utility.

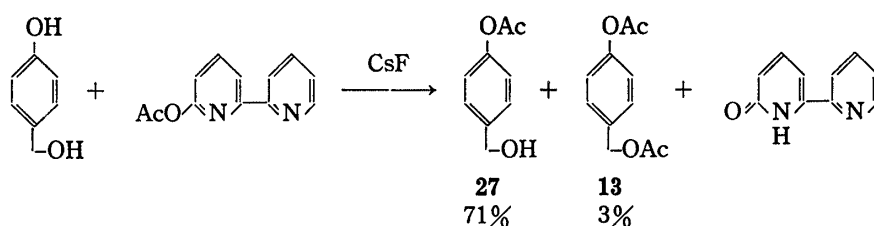


Chart 3

Experimental

Melting points were determined with a Yanagimoto microapparatus. Infrared (IR) spectra were measured on a Jasco A-202 spectrophotometer. Nuclear magnetic resonance (NMR) spectra were taken with Varian T-60 and JEOL JM-FX 100 instruments in CDCl_3 ; signals are given as ppm from TMS as an internal standard. Mass spectra were determined on a JEOL JMS-O1SG double-focusing mass spectrometer. Extracts were dried over anhydrous Na_2SO_4 . A mixture of Kieselgel 60 (70–230 mesh) (Merck) and silicic acid (Mallinckrodt) was used for column chromatography.

Treatment of Oridonin (1) with $\text{Ac}_2\text{O-TlBr}_3 \cdot 4\text{H}_2\text{O}$ — $\text{TlBr}_3 \cdot 4\text{H}_2\text{O}$ (1.420 g, 2.745 mmol) was dissolved in Ac_2O (5 ml) (exothermic!). After cooling to room temperature, the solution was gradually added to a suspension of oridonin (1) (200 mg, 0.549 mmol) in THF (5 ml) with stirring under ice-cooling. After being stirred at room temperature for 15 min, excess cold 5% Na_2CO_3 aqueous solution was added. Extraction with CHCl_3 , washing with brine, drying, and concentration *in vacuo* gave an oily substance, which was purified by chromatography on a silica gel column to afford the diacetate 3 (224 mg, 91.0%) as colorless oil. *Anal.* Calcd for $\text{C}_{24}\text{H}_{32}\text{O}_8$: M, 448.210. Found: M^+ m/e : 448.210. IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 3450–3500, 1725, 1640 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 100 MHz) δ : 0.86, 1.15 (each 3H, s, $\text{CH}_3 \times 2$), 1.99, 2.27 (each 3H, s, $-\text{COCH}_3 \times 2$), 3.06 (1H, d, $J=9.0$ Hz, C-13-H), 3.54 (1H, t, $J=8.0$ Hz, C-1-H), 4.09, 4.35 (each 1H, AB type, $J=10.0$ Hz, C-20- H_2), 5.07 (1H, d, $J=7.0$ Hz, C-6-H), 5.29, 5.98 (each 1H, s, C-17- H_2), 5.87 (1H, s, C-14-H).

Treatment of Oridonin (1) with $\text{Ac}_2\text{O-AlCl}_3$ —A solution of AlCl_3 (366 mg, 2.745 mmol) in Ac_2O (1.5 ml) was added dropwise to a suspension of oridonin (1) (200 mg, 0.549 mmol) in THF (5 ml) with stirring under ice-cooling. After being stirred at room temperature for 2 h, the mixture was treated with a small excess of 5% NaHCO_3 aqueous solution and extracted with CHCl_3 . Usual work-up of the CHCl_3 extract gave an oily substance, which was chromatographed on a silica gel column, eluting successively with CHCl_3 and CHCl_3 -acetone (9:1). The first eluate gave the tetraacetate 4⁷⁾ (34 mg, 11.6%) (colorless needles from MeOH). The second eluate afforded the diacetate 3 (82 mg, 33.3%).

Treatment of Oridonin (1) with $\text{Ac}_2\text{O-BF}_3 \cdot \text{Et}_2\text{O}$ —A solution of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (20 μl , 0.125 mmol) in Ac_2O (1.5 ml) was added dropwise to a suspension of oridonin (1) (200 mg, 0.549 mmol) in THF (5 ml) with stirring under ice-cooling. After being stirred for 1 h under the same conditions, the reaction mixture was quenched by addition of 5% NaHCO_3 aqueous solution. Usual work-up of the reaction mixture gave an oily substance, which was chromatographed on a silica gel column with CHCl_3 -acetone (4:1) to give the diacetate 3 (157 mg, 63.8%) and the monoacetate 2 (56 mg, 25.1%) as colorless needles, mp 230–231°C (from MeOH). *Anal.* Calcd for $\text{C}_{22}\text{H}_{30}\text{O}_7 \cdot \text{H}_2\text{O}$: C, 62.25; H, 7.60; M, 406. Found: C, 62.66; H, 7.44; M^+ m/e : 406. IR $\nu_{\text{max}}^{\text{KBr}}$: 3425, 3285, 1725, 1635 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 100 MHz) δ : 0.89, 1.15 (each 3H, s, $\text{CH}_3 \times 2$), 2.28 (3H, s, $-\text{COCH}_3$), 3.00 (1H, d, $J=8.0$ Hz, C-13-H), 3.54 (1H, t, $J=8.0$ Hz, C-1-H), 4.09, 4.31 (each 1H, AB type, $J=10$ Hz, C-20- H_2), 4.81 (1H, s, C-14-H), 4.98 (1H, d, $J=6$ Hz, C-6-H), 5.32, 5.99 (each 1H, s, C-17- H_2).

Treatment of Oridonin (1) with $\text{Ac}_2\text{O-ZnCl}_2$ —A suspension of ZnCl_2 (374 mg, 2.745 mmol) in Ac_2O (1.5 ml) was added to a suspension of oridonin (1) (200 mg, 0.549 mmol) in THF (5 ml) under ice-cooling. The mixture was stirred for 30 min and treated as usual to recover oridonin (103 mg, 51.5%).

Treatment of Oridonin (1) with $\text{Ac}_2\text{O-Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ —Cupric perchlorate, $\text{Cu}(\text{ClO}_4)_2 \cdot 6\text{H}_2\text{O}$ (1.067 g, 2.745 mmol) was dissolved in Ac_2O (1.5 ml) (exothermic!). After cooling to room temperature, the solution was added dropwise to a suspension of oridonin (1) (200 mg, 0.549 mmol) in THF (5 ml) with stirring under ice-cooling. The reaction mixture was stirred for 30 min at 0°C and for 10 h at room temperature, then usual work-up resulted in the recovery of oridonin (1) (102 mg, 51%).

Treatment of Oridonin (1) with Dodecanoic Anhydride- $\text{BF}_3 \cdot \text{Et}_2\text{O}$ —A solution of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (60 μl , 0.475 mmol) and dodecanoic anhydride (500 mg, 1.309 mmol) in THF (3 ml) was added to a suspension of oridonin (1) (200 mg, 0.549 mmol) in THF (5 ml) with stirring under ice-cooling. The mixture was stirred at room temperature for 18 h and then usual treatment and purification of the resulting crude product on a silica gel column gave oridonin 6-dodecanoate (8) (249 mg, 83%) as colorless oil. *Anal.* Calcd for $\text{C}_{32}\text{H}_{50}\text{O}_7$: M, 546.356. Found: M^+ m/e : 546.357. IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 3600, 3400, 1725, 1700, 1640 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 100 MHz) δ : 0.86 (3H, t, $J=6.1$ Hz, $-\text{CH}_2\text{CH}_3$), 1.22 (6H, s, $\text{CH}_3 \times 2$), 3.53 (1H, t, $J=8.5$ Hz, C-1-H), 4.07, 4.31 (each 1H, AB type, $J=10.0$ Hz, C-20- H_2), 4.81 (1H, s, C-14-H), 4.99 (1H, d, $J=6.0$ Hz, C-6-H), 5.32, 5.97 (each 1H, s, C-17- H_2), 6.02 (1H, s, OH, disappeared with D_2O).

Treatment of Oridonin (1) with Dodecanoic Anhydride-Pyridine—Dodecanoic anhydride (764 mg, 2 mmol) was added to a solution of oridonin (364 mg, 1 mmol) in pyridine (5 ml) with stirring. The mixture was stirred at room temperature for 2 h and then usual treatment yielded oridonin 14-dodecanoate (9) (535 mg, 97.9%) as colorless oil. *Anal.* Calcd for $C_{32}H_{50}O_7$: M, 546.356. Found: $M^+ m/e$: 546.353. IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 3540, 3350, 1740, 1715, 1640 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 100 MHz) δ : 0.84 (3H, t, $J=7.0$ Hz, $-\text{CH}_2\text{CH}_3$), 1.12 (6H, s, $\text{CH}_3 \times 2$), 3.50 (1H, t, $J=8.3$ Hz, C-1-H), 3.77 (1H, dd, $J=11.0$ and 7.0 Hz, C-6-H), 4.06, 4.29 (each 1H, AB type, $J=10.3$ Hz, C-20- H_2), 5.47, 5.80 (each 1H, s, C-17- H_2), 6.12 (1H, s, C-14-H), 6.16 (1H, d, $J=11.0$ Hz, C-6-OH, disappeared with D_2O).

Typical Procedure for Selective Acylation of an Alcoholic Hydroxyl Group—(1) A solution of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (400 μl , 2.5 mmol) in Ac_2O (3.0 ml) was added dropwise to a solution of *p*-hydroxymethylphenol (11) (1.24 g, 10 mmol) in THF (15 ml) under ice-cooling with stirring. After being stirred at 0°C for 4 h, the reaction mixture was treated as usual to give 4-acetoxymethylphenol (12) (1.128 g, 68%)¹⁰ as colorless prisms.

(2) A solution of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (20 μl , 0.125 mmol) in Ac_2O (0.4 ml) was added to a solution of 3,17 β -estradiol (20) (136 mg, 0.5 mmol) in THF (5 ml) under ice-cooling with stirring. After being stirred at 0°C for 4.5 h, usual treatment gave the 17-monoacetate 21 (96 mg, 61.1%)¹¹ as colorless needles from MeOH.

Typical Procedure for Acetylation with Ac_2O -Pyridine—(1) Acetic anhydride (1 ml) was added dropwise to a solution of 4-hydroxymethylphenol (11) (1.24 g, 10 mmol) in pyridine (5 ml) with stirring. The mixture was stirred at room temperature for 3.5 h and an excess of cold 10% HCl aqueous solution was added. The acidic solution was extracted with CH_2Cl_2 . The extract was washed with brine, dried, and concentrated *in vacuo* to leave an oily residue, which was chromatographed on a silica gel column with CH_2Cl_2 to give the diacetate 13 (1.2 g, 62%)^{9,10} as colorless oil.

(2) Acetic anhydride (0.4 ml) was added to a solution of 3,17 β -estradiol (20) (136 mg, 0.5 mmol) in pyridine (1 ml) with stirring. The mixture was stirred at room temperature for 17 h and treated as usual to afford the diacetate 22 (130.1 mg, 73.1%)¹² as colorless flakes from *n*-hexane.

(3) Acetic anhydride (0.4 ml) was added to a solution of 3,17 β -estradiol (20) (136 mg, 0.5 mmol) in pyridine (1 ml) under ice-cooling with stirring. After being stirred at 0°C for 1 h, usual work-up of the reaction mixture gave an oily substance, which was chromatographed on a silica gel column with CHCl_3 -acetone (10:1) to give the diacetate 22 (6 mg, 3.4%) and the monoacetate 23 (99 mg, 63.1%)¹³ as colorless needles from *n*-hexane-ether.

Physical Data for Each Acetate—4-Acetoxymethylphenol (12): colorless prisms, mp $80-81^\circ\text{C}$ (from H_2O) (lit.¹⁰ 84°C). *Anal.* Calcd for $\text{C}_9\text{H}_{10}\text{O}_3$: M, 166.063. Found: $M^+ m/e$: 166.061. IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 3610, 3350, 3040, 1720, 1615 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ : 2.07 (3H, s, $-\text{COCH}_3$), 5.03 (2H, s, CH_2OAc), 6.82, 7.18 (each 2H, AB type, $J=8.0$ Hz, aromatic protons).

4-Acetoxymethylphenol Acetate (13): bp $105^\circ\text{C}/5$ mm colorless oil (lit.¹⁰ bp $155-157^\circ\text{C}/11$ mm). *Anal.* Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_4$: M, 208.074. Found: $M^+ m/e$: 208.074. IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 3020, 1717, 1600 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ : 3.07, 3.27 (each 3H, s, $-\text{COCH}_3 \times 2$), 5.07 (2H, s, $-\text{CH}_2\text{OAc}$), 7.06, 7.30 (each 2H, AB type, $J=9$ Hz, aromatic protons).

4-Acetoxymethyl-2-methoxyphenol (15): Pale yellow oil. *Anal.* Calcd for $\text{C}_{10}\text{H}_{12}\text{O}_4$: M, 196.074. Found: $M^+ m/e$: 196.075. IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 3540, 3010, 1730, 1605 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ : 2.08 (3H, s, $-\text{COCH}_3$), 3.88 (3H, s, OCH_3), 5.02 (2H, s, $-\text{CH}_2\text{OAc}$), 6.87 (3H, s, aromatic protons).

4-Acetoxymethyl-2-methoxyphenol Acetate (16): Colorless needles, mp $42-44^\circ\text{C}$ (from MeOH). *Anal.* Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_5$: C, 60.50; H, 5.92; M, 238. Found: C, 60.61; H, 6.01; $M^+ m/e$: 238. IR $\nu_{\text{max}}^{\text{KBr}}$: 1760, 1735 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ : 2.03, 2.23 (each 3H, s, $-\text{COCH}_3 \times 2$), 3.77 (3H, s, OCH_3), 5.00 (2H, s, $-\text{CH}_2\text{OAc}$), 7.27 br (3H, aromatic protons).

4-(3-Acetoxypropyl)phenol (18): Colorless oil. *Anal.* Calcd for $\text{C}_{11}\text{H}_{14}\text{O}_3$: M, 194. Found: $M^+ m/e$: 194. IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 3600, 3350, 1722 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 60 MHz) δ : 1.96 (2H, m, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 2.01 (3H, s, $-\text{COCH}_3$), 2.57 (2H, t, $J=8.0$ Hz, $\text{ArCH}_2\text{CH}_2-$), 4.04 (2H, t, $J=6.5$ Hz, $-\text{CH}_2\text{OAc}$), 5.56 br (1H, s, $-\text{OH}$, disappeared with D_2O), 6.58, 6.91 (each 2H, AB type, $J=8.0$ Hz, aromatic protons).

4-(3-Acetoxypropyl)phenol Acetate (19):¹⁴ Colorless oil. *Anal.* Calcd for $\text{C}_{13}\text{H}_{16}\text{O}_4$: M, 236. Found: $M^+ m/e$: 236. IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 1750, 1730 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 100 MHz) δ : 1.99 (2H, m, $-\text{CH}_2\text{CH}_2\text{CH}_2-$), 2.00, 2.24 (each 3H, s, $-\text{COCH}_3 \times 2$), 2.65 (2H, t, $J=8.0$ Hz, $\text{ArCH}_2\text{CH}_2-$), 4.06 (2H, t, $J=6.5$ Hz, $-\text{CH}_2\text{OAc}$), 6.97, 7.19 (each 2H, AB type, $J=8.0$ Hz, aromatic protons).

3,17 β -Estradiol 17-Acetate (21): Colorless needles, mp $207-208^\circ\text{C}$ (from MeOH) (lit.¹¹ $212-215^\circ\text{C}$). *Anal.* Calcd for $\text{C}_{20}\text{H}_{26}\text{O}_3$: C, 76.40; H, 8.34; M, 314.188. Found: C, 76.01; H, 8.49; $M^+ m/e$: 314.188. IR $\nu_{\text{max}}^{\text{KBr}}$: 3445, 1705, 1620 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 100 MHz) δ : 0.81 (3H, s, CH_3), 2.03 (3H, s, $-\text{COCH}_3$), 4.67 (1H, t, $J=8.0$ Hz, C-17-H), 4.94 br (1H, s, OH, disappeared with D_2O), 6.55 br s (1H, M part of ABM type, C-4-H), 6.60 (1H, B part of ABM type, $J=8.0$ and 3.0 Hz, C-2-H), 7.12 (1H, A part of ABM type, $J=8.0$ Hz, C-1-H).

3,17 β -Estradiol Diacetate (22): Colorless needles, mp $125-126^\circ\text{C}$ (from *n*-hexane) (lit.¹² $123-125^\circ\text{C}$). *Anal.* Calcd for $\text{C}_{22}\text{H}_{28}\text{O}_4$: C, 74.13; H, 7.92; M, 356.199. Found: C, 74.17; H, 8.10; $M^+ m/e$: 356.198. IR $\nu_{\text{max}}^{\text{KBr}}$: 1762, 1728 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 , 100 MHz) δ : 0.83 (3H, s, CH_3), 2.05, 2.28 (each 3H, s, $-\text{COCH}_3 \times 2$), 4.66 (1H, t, $J=8.0$ Hz, C-17-H), 6.78 br s (1H, M part of ABM type, C-4-H), 6.82 (1H, B part of ABM type, $J=7.5$ and 3.0 Hz, C-2-H), 7.30 (1H, A part of ABM type, $J=7.5$ Hz, C-1-H).

3,17 β -Estradiol 3-Acetate (23): Colorless needles, mp 132—133°C (from *n*-hexane-ether) (lit.¹³) 134—136°C). *Anal.* Calcd for C₂₀H₂₈O₃: C, 76.40; H, 8.34; M, 314.188. Found: C, 76.27; H, 8.55; M⁺ *m/e*: 314.187. IR $\nu_{\text{max}}^{\text{KBr}}$: 3520, 1740 cm⁻¹. ¹H-NMR (CDCl₃, 100 MHz) δ : 0.77 (3H, s, CH₃), 2.25 (3H, s, -COCH₃), 3.71 (1H, t, *J*=8.0 Hz, C-17-H), 6.77 br s (1H, M part of ABM type, C-4-H), 6.81 (1H, B part of ABM type, *J*=8.0 and 3 Hz, C-2-H), 7.25 (1H, A part of ABM type, *J*=8.0 Hz, C-1-H).

3,16 α ,17 β -Estriol 16,17-Diacetate (25): Colorless needles, mp 173—175°C (from MeOH) (lit.¹¹) 171—173°C). *Anal.* Calcd for C₂₂H₂₈O₅: M, 372. Found: M⁺ *m/e*: 372. IR $\nu_{\text{max}}^{\text{CHCl}_3}$: 3620, 1735, 1610 cm⁻¹. ¹H-NMR (CDCl₃, 100 MHz) δ : 0.82 (3H, s, CH₃), 2.02, 2.04 (each 3H, s, -COCH₃ × 2), 4.98 (1H, d, *J*=5.0 Hz, C-17-H), 5.19 (1H, m, C-16-H), 5.82 br (1H, s, OH, disappeared with D₂O), 6.56 br s (1H, M part of ABM type, C-4-H), 6.63 (1H, B part of ABM type, *J*=8.0 and 3.0 Hz, C-2-H), 7.10 (1H, A part of ABM type, *J*=8.0 Hz, C-1-H).

3,16 α ,17 β -Estriol Triacetate (26): Colorless plates, mp 121—123°C (from MeOH) (lit.¹⁵) 125—127°C). *Anal.* Calcd for C₂₄H₃₀O₆: C, 69.54; H, 7.30; M, 414. Found: C, 69.69; H, 7.45; M⁺ *m/e*=414. IR $\nu_{\text{max}}^{\text{KBr}}$: 1770, 1760, 1735 cm⁻¹. ¹H-NMR (CDCl₃, 100 MHz) δ : 0.82 (3H, s, CH₃), 2.02, 2.04, 2.24 (each 3H, s, -COCH₃ × 3), 4.98 (1H, d, *J*=4.0 Hz, C-17-H), 5.19 (1H, m, C-16-H), 6.77 br s (1H, M part of ABM type, C-4-H), 6.81 (1H, B part of ABM type, *J*=8.0 and 3.0 Hz, C-2-H), 7.22 (1H, A part of ABM type, *J*=8.0 Hz, C-1-H).

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