Regioselective Acetylation of 2-Aryl-2-butene-1,4-diols and Hydrolysis of Their Diacetates Using Porcine Pancreas Lipase

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Acetylation of 2-aryl-2-butene-1,4-diols with 10 equivalents of vinyl acetate in the presence of 50 wt % of porcine pancreas lipase (PPL) Type II regioselectively proceeded to afford the corresponding 3-aryl-4-hydroxy-2-butenyl acetates in 83–93% yields. Hydrolysis of 2-aryl-2-butene-1,4-diyl diacetates in the presence of 100 wt % of PPL Type II regioselectively afforded the corresponding 2-aryl-4-hydroxy-2-butenyl acetates in 68–95% yields.

Substituted 2-butene-1,4-diols are potentially useful intermediates in organic synthesis.[1] Regioselective protection of substituted 2-butene-1,4-diols by acetyl group using lipase PS-D has been reported only by Takabe and co-workers.[2] In this method, acetylation and hydrolysis of 2-methyl-2-butene-1,4-diols and their acetates afforded the corresponding monoacetates in moderate yields (27–63%) because undesirable by-products were obtained in all cases. We have recently reported preparation of 3-substituted (*E*)-2-hydroxymethyl-2-propenyl acetates by regiospecific acetylation[3] of 2-alkylidene-1,3-propanediols containing substituted benzene, polycyclic, or heterocyclic aromatic rings with vinyl acetate using porcine pancreas lipase (PPL) Type II. Furthermore, we have developed preparation of 3-substituted (*Z*)-2-hydroxymethyl-2-propenyl acetates by highly regioselective hydrolysis[4] of 2-alkylidenepropane-1,3-diyl diacetates using PPL Type II. Our method has been found to be convenient for the preparation of the monoacetates of substituted 2-butene-1,4-diols. In this paper, we describe both of a regioselective acetylation of 2-aryl-2-butene-1,4-diols **1a**–**1g** with vinyl acetate using 50 wt % of PPL Type II and a regioselective hydrolysis of 2-aryl-2-butene-1,4-diyl diacetates **2a**–**2g** in the presence of 100 wt % of PPL Type II.

The diacetates **2a**–**2g** were easily prepared from arylboronic acid and 2-butyne-1,4-diyl diacetates by the Suzuki reaction in 20–73% yields.[5] Then, the diols **1a**–**1g** were obtained by hydrolysis of **2a**–**2g** in 72–97% yields.

In a preliminary investigation, the reaction of 2-phenyl-2-butene-1,4-diol (**1a**) with vinyl acetate in the presence of 50 wt % of PPL Type II in 1,4-dioxane afforded 3-phenyl-4-hydroxy-2-butenyl acetate (**3a**)[6] in 91% yield as indicated in Entry 1 of Table 1. The diacetate **2a** was produced as a by-product in 3.1% yield, and the starting material **1a** and 2-phenyl-4-hydroxy-2-butenyl acetate (**4a**) were not detected from ^{1}H NMR analysis of the crude product. The regioselective acetylation of 2-aryl-2-butene-1,4-diols substituted on the benzene ring by electron-donating or electron-withdrawing groups was then examined: the results from the acetylation of various 2-aryl-2-butene-1,4-diols **1b**–**1g** with vinyl acetate in the presence of 50 wt % of PPL in 1,4-dioxane are shown in Table 1. We selected methoxy and methyl substituents as representative electron-donating groups (Entries 2, 3, 6, and 7) or fluoro and chloro substituents as electron-withdrawing groups (Entries 4 and 5). Fortunately, all 2-aryl-2-butene-1,4-diols **1b**–**1g** reacted with vinyl acetate in the presence of 50 wt % of PPL in 1,4-dioxane to afford the corresponding 3-aryl-4-hydroxy-2-butenyl acetates **3b**–**3g** in excellent yields with high regioselectivities. The 2-aryl monoacetates **4b**–**4g** were not detected from the crude products in all entries of Table 1.

Next, the reaction of 2-phenyl-2-butene-1,4-diyl diacetate (**2a**) in the presence of 100 wt % of PPL in a 1:1 mixture of DMSO (dimethyl sulfoxide)–PB (1/15 M phosphate buffer, pH 7.0) afforded the corresponding 2-phenyl monoacetate **4a**[7] in 89% yield as indicated in Entry 1 of Table 2. The diol **1a** was produced as a by-product in 1.2% yield and the starting material **2a** was recovered in 1.2% yield. The 3-phenyl monoacetate **3a** was not detected from ^{1}H NMR analysis of the crude product. The regioselective hydrolysis of 2-aryl-2-butene-1,4-diyl diacetates substituted on the benzene ring by electron-donating or electron-withdrawing groups was examined: the results from hydrolysis of various substituted 2-aryl-2-butene-1,4-diyl diacetates **2b**–**2g** in the presence of 100 wt % of PPL in a 1:1 mixture of DMSO–PB are shown in Table 2. We selected methoxy and methyl substituents as representative electron-donating groups (Entries 2, 3, 6, and 7) or fluoro and chloro substituents as electron-withdrawing groups (Entries 4 and 5). Fortunately, all 2-aryl-2-butene-1,4-diyl diacetates **2b**–**2g** reacted in the presence of 100 wt % of PPL in a 1:1 mixture of DMSO–PB to afford the corresponding 2-aryl monoacetates in good to excellent yields with high regioselectivities. The 3-aryl monoacetates **3b**–**3g** were not detected from the crude products in all entries of Table 2.

In summary, porcine pancreas lipase (PPL) Type II efficiently works as a catalyst both in acetylation of 2-aryl-2-butene-1,4-diols **1** and in hydrolysis of 2-aryl-2-butene-1,4-diyl diacetates **2**. In our procedure, it is possible to prepare various 2- or 3-aryl-4-hydroxy-2-butenyl acetates. The products are useful synthetic intermediates and we have already succeeded the total synthesis of racemic milnacipran,[8] which is a commercially available medicine as a serotonin noradrenaline reuptake inhibitor (SNRI). We are still working on asymmetric synthesis of milnacipran.

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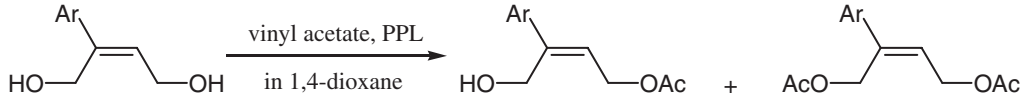
Table 1. Acetylation of 2-aryl-2-butene-1,4-diols **1a**–**1g** in the presence of PPL[a]

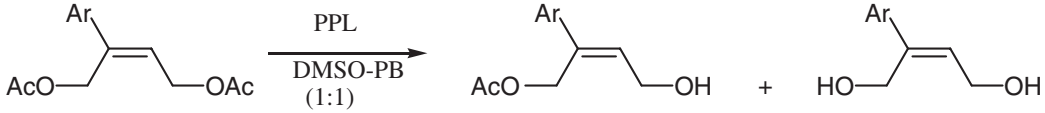


1 **3** **2**

Entry	**1**	Ar	**3**/%	Recovery **1**/%	Diacetate **2**/%
1	**1a**	Ph	91	N.D.[b]	3.1
2	**1b**	4-$MeOC_6H_4$	89	2.8	trace
3	**1c**	4-MeC_6H_4	91	N.D.	N.D.
4	**1d**	4-FC_6H_4	93	N.D.	4.1
5	**1e**	4-ClC_6H_4	83	N.D.	2.9
6	**1f**	3-MeC_6H_4	90	N.D.	2.7
7	**1g**	2-MeC_6H_4	88	3.7	trace

[a]All reactions were carried out with 1 mmol of 2-aryl-2-butene-1,4-diol **1**, 10 mmol of vinyl acetate, and 50 wt % of PPL in 3 mL of 1,4-dioxane at rt for 24 h. [b]Not detected.

Table 2. Hydrolysis of 2-aryl-2-butene-1,4-diyl diacetates **2a**–**2g** in the presence of PPL[a]



2 **4** **1**

Entry	**2**	Ar	**4**/%	Recovery **2**/%	Diol **1**/%
1	**2a**	Ph	89	1.2	1.2
2	**2b**	4-$MeOC_6H_4$	78	7.2	1.8
3	**2c**	4-MeC_6H_4	77	13	6.6
4	**2d**	4-FC_6H_4	94	N.D.[b]	4.9
5	**2e**	4-ClC_6H_4	68	22	6.5
6	**2f**	3-MeC_6H_4	74	11	5.5
7	**2g**	2-MeC_6H_4	95	N.D.	N.D.

[a]All reactions were carried out with 1 mmol of 2-aryl-2-butene-1,4-diyl diacetate **2** and 100 wt % of PPL in 6 mL of a 1:1 mixure of DMSO–PB at rt for 48 h. [b]Not detected.

References and Notes

1 a) J. H. Hong, S.-Y. Kim, C.-H. Oh, K. H. Yoo, J.-H. Cho, *Nucleosides Nucleotides Nucleic Acid* **2006**, *25*, 341. b) A. Kim, J. H. Hong, *Bull. Korean Chem. Soc.* **2006**, *27*, 976, and the references cited therein.

2 K. Takabe, N. Mase, T. Hisano, H. Yoda, *Tetrahedron Lett.* **2003**, *44*, 3267, and the references cited therein.

3 a) T. Miura, K. Okazaki, K. Ogawa, E. Otomo, S. Umetsu, M. Takahashi, Y. Kawashima, Y. Jyo, N. Koyata, Y. Murakami, N. Imai, *Synthesis* **2008**, 2695. b) T. Miura, Y. Kawashima, M. Takahashi, Y. Murakami, N. Imai, *Synth. Commun.* **2007**, *37*, 3105.

4 a) T. Miura, S. Umetsu, D. Kanamori, N. Tsuyama, Y. Jyo, Y. Kawashima, N. Koyata, Y. Murakami, N. Imai, *Tetrahedron* **2008**, *64*, 9305. b) T. Miura, Y. Kawashima, S. Umetsu, D. Kanamori, N. Tsuyama, Y. Jyo, Y. Murakami, N. Imai, *Chem. Lett.* **2007**, *36*, 814.

5 A. K. Gupta, K. S. Kim, C. H. Oh, *Synlett* **2005**, 457.

6 A typical procedure of acetylation using PPL Type II is as follows. To a pale yellow suspension of 164 mg (1.00 mmol, 1 equivalent) of 2-phenyl-2-butene-1,4-diol (**1a**), 0.92 mL (10.0 mmol, 10 equivalent) of vinyl acetate, and 82 mg (50 wt %) of PPL in 3 mL of 1,4-dioxane was stirred at rt for 24 h. The reaction suspension was diluted with 10 mL of ethyl acetate and anhydrous magnesium sulfate was added. The mixture was filtered, and the filtrate was evaporated. The crude product was chromatographed on silica gel with a 1:2 mixture of ethyl acetate and hexane to afford 187 mg (91% yield) of **3a**. **3a**: ^{1}H NMR ($CDCl_3$): δ 2.08 (3H, s), 2.48 (1H, t, $J = 5.9$ Hz), 4.60 (2H, d, $J = 5.9$ Hz), 4.88 (2H, d, $J = 7.4$ Hz), 5.92 (1H, t, $J = 7.4$ Hz), 7.28–7.51 (5H, m); ^{13}C NMR ($CDCl_3$): δ 21.1, 60.1, 61.2, 124.3, 126.4, 128.0, 128.6, 140.1, 143.9, 171.5.

7 A typical procedure of hydrolysis using PPL Type II is as follows. To a pale yellow suspension of 248 mg (1.00 mmol, 1 equivalent) of 2-phenyl-2-butene-1,4-diyl diacetate (**2a**) and 248 mg (100 wt %) of PPL in 6 mL of a 1:1 mixture of DMSO–PB (pH 7.0) was stirred at rt for 48 h. The reaction mixture was filtered on Celite, and washed with ethyl acetate. The filtrate was added to water, and then extracted three times with ethyl acetate. The combined ethyl acetate layers were washed with brine, and dried over anhydrous magnesium sulfate. The mixture was filtered, and the filtrate was evaporated. The crude product was chromatographed on silica gel with a 1:2 mixture of ethyl acetate and hexane to afford 183 mg (89% yield) of **4a**. **4a**: ^{1}H NMR ($CDCl_3$): δ 2.01 (3H, s), 2.12 (1H, brs), 4.43 (2H, d, $J = 6.9$ Hz), 5.08 (2H, s), 6.22 (1H, t, $J = 6.9$ Hz), 7.28–7.44 (5H, m); ^{13}C NMR ($CDCl_3$): δ 21.0, 59.0, 61.1, 126.3, 127.8, 128.5, 132.2, 136.6, 139.6, 171.3.

8 H. Fujimori, T. Noguchi, M. Kawasaki, K. Akimoto, N. Imai, M. Kirihara, unpublished data.

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