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Selective monodeacetylation of methyl 2,3,5-tri-*O*-acetyl-D-arabinofuranoside using biocatalyst

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Abstract—Methyl arabinofuranoside **1** was fully acetylated to methyl 2,3,5-tri-*O*-acetyl-D-arabinofuranoside **2** and it was regioselectively deacetylated using enzymes. *Rhizopus oryzae* esterase gave methyl 3,5-di-*O*-acetyl-D-arabinofuranoside **3**, regioselectively. This protected **3** was deoxygenized to 3,5-di-*O*-acetyl-D-2-deoxyarabinofuranoside **7** using hypophosphorous acid.

Carbohydrates containing polyhydroxyl groups are inexpensive and have the important biological and physical functions. Their inherent stereochemistries have been utilized to construct the applied molecular scaffolds such as pharmaceuticals,[1] surfactants[2] and functional polymers.[3] But these compounds are difficult to manipulate regioselectively because of their similar reactivities. Thus selective protection/deprotection steps are needed, conventionally.[4] Methyl arabinofuranoside **1** and its C-2 functionalized analogue are useful for the synthesis of polysaccharides such as arabinogalactan and lipoarabinomannan.[5] Especially, 2-deoxyarabinofuranoside can be used as precursor for the synthesis of various nucleosides as antiviral agent. To do this work, the C-2 deoxygenation of compound **1** should be performed regioselectively. As estimated, there is no major product as mono-deacetylation in case of using inorganic acids or bases. Biocatalysts have been used to synthesize the various organic compounds under the aqueous or non-aqueous media[6] and their reaction specificity can differentiate the similar hydroxyl groups, regioselectively. Wong and co-workers[7] used hydrolases in the synthesis of furanose, pyranose and other derivatives by the regioselective protection and deprotection method. This letter was focused on the regioselective deacylation of monosaccharide, 2,3,5-tri-*O*-acetyl-D-arabinofuranoside **2** using biocatalysts and the product 3,5-di-*O*-acetyl-D-arabinofuranoside **3** was chemically transformed to 3,5-di-*O*-acetyl-D-2-deoxyarabinofuranoside **7** as precursor for the synthesis of chiral synthons.

To select ones for C-2 selective deprotection of compound **2**, various enzymes were screened and these hydrolyzed products **3**, **4** and **5** were mixtures as presented in Table 1. At first, the blank test was tested in the aqueous phosphate buffer solution (pH 7) without enzyme. In this reaction, compound **2** was hydrolyzed at C-2 moderately although the reaction was long (62 h). In enzymatic reaction as Scheme 1, most of them hydrolyzed it at the secondary alcohol C-2 ester except the lipase from *Candida rugosa*, which was acting at the primary alcohol C-5 ester. These results might come from the favourable substrate–enzyme complex[8] in addition to the result of blank test. Pig liver esterase completely hydrolyzed it within 1 h and C-2 hydrolyzed compound **3** was obtained at 70%. For our purpose, esterases from *Rhizopus oryzae*, pig liver and lipases from hog pancreas and *R. oryzae* were adequate. But

Table 1. Distributions of product from hydrolysis of compound **2**

Enzyme	Reaction time (h)	**2** (%)	**3** (%)	**4** (%)	**5** (%)
Rhizopus oryzae lipase (LRO)	38	32	53	1	2
Candida rugosa lipase (CRL)	13	6	1	2	79
Pig liver esterase (PLE)	1	—	70	2	6
Hog pancreas lipase (HPL)	3	25	44	9	3
Wheat germ lipase (LWG)	0.5	51	33	7	—
Rhizopus niveus lipase (LN)	83	69	17	3	—
Rhizopus oryzae esterase (ERO)	7	4	86	3	1
Blank	62	74	9	5	3

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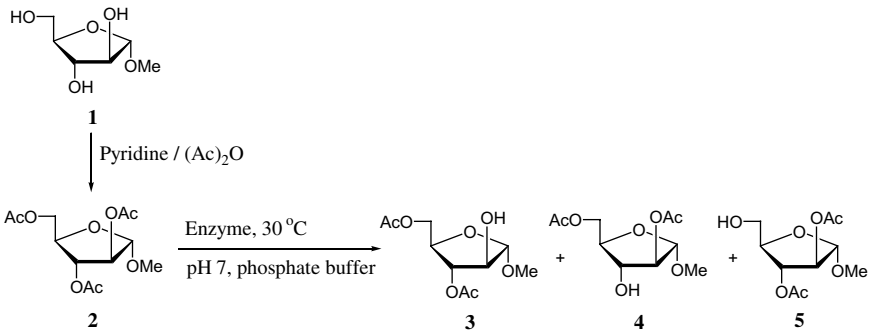


Scheme 1. Enzymatic deacetylation of 2,3,5-tri-*O*-acetyl-D-arabinofuranoside **2**.

the reaction rate of two lipases were relatively low and gave the unwanted by-products **4** and **5**. Therefore, the two esterases from *R. oryzae* and pig liver were confined to optimize the reaction condition.

During the investigation, the solvent effect was highly critical to obtain the C-2 deacetylated compound **3**. We used the solvents as additive and the composition was 9/1 (aqueous phosphate buffer/organic solvent). The results from using the various solvents are shown in Table 2. In most solvents, compound **3** was obtained predominantly by ERO and PLE. Especially, in dimethylsulfoxide, *n*-hexane and *t*-butanol, the esterase ERO almost gave compound **3**.

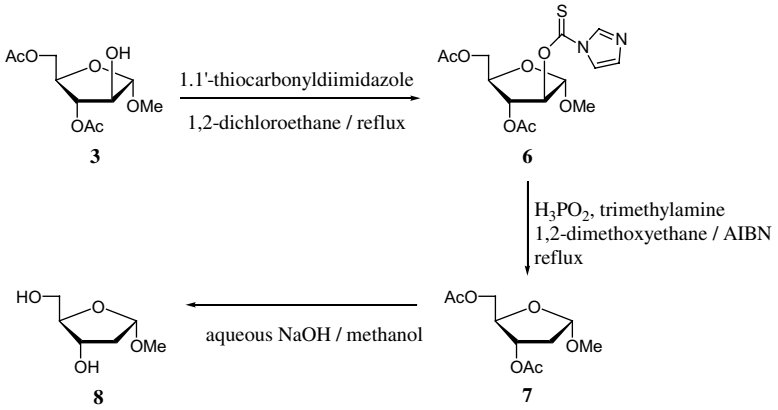
Therefore, we used the aqueous buffer solution/dimethyl sulfoxide (9/1) as solvent and *R. oryzae* esterase to get the 3,5-di-*O*-acetyl-D-arabinofuranoside **3**. This is a protected precursor for the 2-deoxygenized compound **7**. Scheme 2 shows the procedure to synthesize compound **7** by free radical deoxygenation. The original method was developed by Barton and McCombie[9] and many other researches have modified it. Generally, in this reaction, tri-*n*-butyltin hydride ($^{n}Bu_3SnH$) was used as the reducing agent. But in our substrate **3**, the resulted major product was methyl 2,3,5-tri-*O*-acetyl-2-*O*-butyl-D-arabinofuranoside by *n*-butyl group transfer from $^{n}Bu_3SnH$. Thus we used hypophosphorous acid instead of tin derivative.[10]

The coupling reaction between compound **3** and 1,1′-thiocarbonyldiimidazole occurred smoothly under the 1,2-dichloroethane reflux and nitrogen atmosphere as shown in Scheme 2. There were no side products and

Table 2. Solvent effects on hydrolysis of 2,3,5-tri-*O*-acetyl-D-arabinofuranoside **2** by ERO and PLE

Solvent[a]	**2** (%)		**3** (%)		**4** (%)		**5** (%)	
	ERO	PLE	ERO	PLE	ERO	PLE	ERO	PLE
Dimethyl sulfoxide	—		100	94.6	—	0.9	—	1.7
N,*N*-Dimethyl formamide	53.5		38.1	88.4	0.9	2.7	—	6.7
t-Butanol	59.5	15.6	37.9	75	—	0.8	—	4.3
Acetone	7.6	1.1	91.2	76.7	—	6	—	12.7
Tetrahydrofuran	89.1	20.9	8.7	69.4	0.8	0.9	—	5.2
Methylene chloride	2.5	55.1	88.5	—	2.3	28.2	0.8	6
n-Hexane	3.7	—	93.2	74.4	—	14.2	—	—
Only buffer solution	63.6		33	90.1	0.7	4.8	—	1.3

[a] Solvent was used as additive (9/1 = aqueous buffer solution/organic solvent).



Scheme 2. 2-Deoxygenation of the protected compound **3**.

the purified product **6** was obtained in 90% yield as a syrup. This protected product was subjected to radical deoxygenation. Compound **6** and trimethylamine in dimethoxyethane were stirred and 50% aqueous hypophosphorous acid was added. The reaction mixture was heated until reflux, then α,α′-azobisisobutyronitrile (AIBN) in dimethoxyethane was added dropwise in three portions. After 2 h, the starting material disappeared completely.[11] This method was free of methyl 2,3,5-tri-*O*-acetyl-2-*O*-butyl-D-arabinofuranoside and the work-up procedure, and the yield was up to 60%. Finally, this compound **7** was hydrolyzed to compound **8** quantitatively and identified with the reported spectral data.

In conclusion, we obtained the protected 2-D-deoxyribose from naturally abundant D-arabinose as moderate yield. D-Arabinose was chemically transformed to methyl 2,3,5-tri-*O*-acetyl-D-arabinofuranoside **2** and C-2 regioselective deacetylation was performed using *R. oryzae* esterase. This enzyme showed very high regioselectivity and 2-deacetylated product was obtained quantitatively as compound **3**. Finally, it was deoxygenized by free radical reaction and the products **7** and **8** will be on going to prepare nucleoside antiviral agents and chiral drug intermediates.

Acknowledgements

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11. (a) Synthesis of compound **6**: A solution of methyl 2,3-di-*O*-acetyl-D-arabinofuranoside **3** (100 mg, 0.4 mmol) and 1.1′-thiocarbonyldiimidazole (140 mg, 0.81 mmol) in anhydrous 1,2-dichloroethane (3 ml) was refluxed under nitrogen atmosphere for 3 h. After cooling to room temperature, the solvent was removed under the reduced pressure. The residue was chromatographed on a column of silica gel with a stepwise gradient of ethyl acetate/*n*-hexane to give compound **6** as a syrup (130 mg, 90%). $[\alpha]_D^{22}$ +56.9 (*c* 0.93, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 2.07 (s, 3H), 2.15 (s, 3H), 3.46 (s, 3H), 4.26–4.32 (m, 2H), 4.47–4.51 (m, 1H), 5.16 (s, 1H), 5.21–5.23 (m, 1H), 5.69 (d, 1H, J = 1.32 Hz), 7.05–7.06 (m, 1H), 7.61–7.62 (m, 1H); ^{13}C NMR δ 20.6, 20.7, 55.1, 62.8, 76.3, 80.2, 88.7, 105.8, 117.9, 131.1, 136.9, 170, 170.5; (b) Synthesis of compound **7**: To a solution of compound **6** (50 mg, 0.14 mmol) in dimethoxyethane (2.5 ml) were added triethylamine (0.23 ml, 1.7 mmol) and 50% aqueous hypophosphorous acid (0.15 ml, 1.4 mmol). The reaction mixture was refluxed with heating and AIBN (14 mg, 0.08 mmol) dissolved in dimethoxyethane (1.5 ml) was added in three portions. After stirring for 2 h at reflux, the reaction mixture was cooled to room temperature. The organic layer was concentrated under the reduced pressure and the residue was chromatographed on a column of silica gel with an eluent solvent ethyl acetate/*n*-hexane to give compound **7** as syrup (82 mg, 60%). $[\alpha]_D^{24}$ +121 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$): δ 1.96–2.02 (m, 1H), 2.07 (s, 6H), 2.33–2.42 (m, 1H), 3.37 (s, 3H), 4.16 (dd, 1H, J = 4.7, 11.4 Hz), 4.92 (s, 1H), 5.03 (m, 1H), 5.10 (m, 1H); ^{13}C NMR δ 20.8, 21.0, 39.0, 55.1, 63.9, 73.9, 80.5, 104.9, 170.6, 170.9.