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Synthesis of hexopyranosyl acetates and 2,3-disubstituted tetrahydropyrans via chemoselective hydrogenation of hex-2-enopyranosyl acetates

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Abstract—A simple and easy method for chemoselective synthesis of hexopyranosyl acetates and 2,3-disubstituted tetrahydropyrans from hex-2-enopyranosyl acetates was demonstrated. The former was achieved by hydrogenation catalyzed by Rh/Al_2O_3 in EtOAc/toluene solvent at 0 °C, while the latter was carried out using Pd/C in EtOH/AcOH at 25 °C.

Carbohydrates are most promising, naturally occurring, raw materials mainly because of their environmentally sustainable use and their enantio- and diastereomerical purity. We have so far been working on their fundamental and important chemical conversions, O- and C-glycosidations, some of which are ecologically friendly processes within the ambit of '*Green Carbohydrate Chemistry*'.[1] But although carbohydrates are attractive as starting materials for enantio- and diastereomerically pure compound syntheses,[2] their highly oxygenated nature is sometimes regarded as an inconvenience due to the need for appropriate deoxygenation in order to obtain materials with desired functionalization. In this context, we have demonstrated, through easy, simple, and classical reactions, a novel chemoselective method of preparation of highly deoxygenated sugar donors and chiral tetrahydropyrans by hydrogenation.[3]

In the course of our synthetic studies of vineomycin B_2,[4] an anthracycline antibiotic, we found an interesting reduction reaction of hex-2-enopyranosyl acetate **1**,[5] which yields the desired hexopyranosyl acetate **2** accompanied by 2,3-disubstituted tetrahydropyran **3** (Scheme 1). Compound **2** and its family must work as glycosyl donors of 2,3-deoxy sugars found in vineomycin B_2, whereas the reductant by two H_2, **3**, can be used as a chiral material. For example, 2,3-disubstituted chiral tetrahydropyran derived from glucose has been used for the total synthesis of brevetoxin B.[6] These results prompted us to examine the chemoselective hydrogenations of hex-2-enopyranosyl acetates to selectively produce hexopyranosyl acetates or 2,3-disubstituted tetrahydropyrans.

We first screened several catalysts generally used: 10% Pd/C, 20% $Pd(OH)_2/C$ (Pearlman's catalyst), 10% Pt/C, Raney-Ni, and 5% Rh/Al_2O_3, for the hydrogenations of the hex-2-enopyranosyl acetate **4** with a hydrogen balloon in EtOH at 25 °C for 1 h (entries 1–5 in Table 1). It was found that the 2,3-disubstituted tetrahydropyran **6** was produced in good yield in preference to the hexopyranosyl acetate **5** with Pd/C or $Pd(OH)_2/C$. Pd/C and $Pd(OH)_2/C$ have comparable efficiencies for this deoxygenation reaction at the C-1 position of **4**, but the latter also gave glycoside **7**, which probably resulted from anomeric activation of **4** or **5** by the Lewis acidity of $Pd(OH)_2/C$ and then coupling with the solvent, EtOH.[7] Therefore, of the five catalysts examined, we considered Pd/C to be the best for obtaining 2,3-disubstituted tetrahydropyrans. In contrast, **5** was obtained in a slightly greater yield than **6** with Rh/Al_2O_3. Thus, it was confirmed that Rh/Al_2O_3 was suitable for converting hex-2-enopyranosyl acetates into the corresponding hexopyranosyl acetates. Hydrogenation, especially when catalyzed by Pd, may show a tendency to eliminate an allylic heteroatom substituent hydrogenolytically via a π-allyl palladium complex.

Keywords: Hydrogenation; Hydrogenolysis; Carbohydrates; Chemoselectivity; Tetrahydropyrans.
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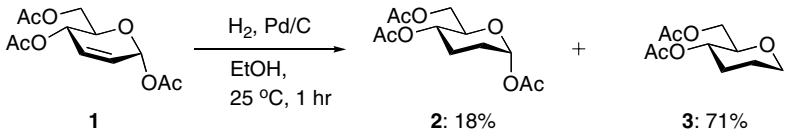


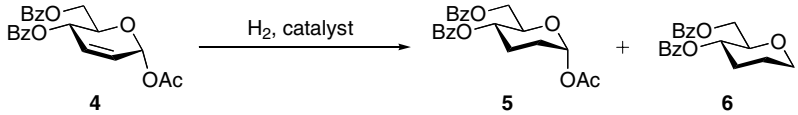
Scheme 1. Hydrogenation of **1**.

Indeed, Tsuji and Yamakawa reported the preparation of 1-olefins by the palladium-catalyzed transfer hydrogenolysis of allylic acetates with ammonium formates.[8] However, no products resulting from cleavage of the allylic benzoate or the cyclic allylic ether were isolated in these entries.

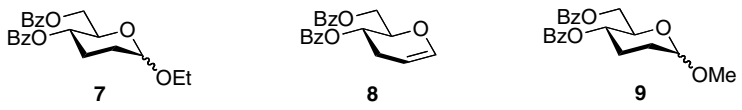
With the preliminary results in hand, we next optimized the reaction conditions, including solvents, reaction temperature, and reaction time, to selectively obtain tetrahydropyran **6** (entries 6–9 in Table 1). It was found that the hydrogenation catalyzed by Pd/C with EtOH gave better yields of **6** than with THF, EtOAc, and MeOH. Furthermore, acidic conditions, using EtOH/AcOH (9/1, v/v) as a solvent to enhance elimination of an acetoxy group, worked well, giving **6** in good yield with good chemoselectivity. At this stage, we further confirmed the following phenomena, as shown in Scheme 2. The hydrogenation conditions did not affect the anomeric acetate of the saturated pyranosyl acetate **5** (Eq. 1 in Scheme 2). Therefore, it is clear that the double bond at the C-2 position is the prerequisite for the cleavage of anomeric acetate. In addition, since methyl glycoside **10** gave only one H_2 adduct **11** under these conditions, the two H_2 reduction requires a substituent at the C-1 position having appropriate leaving ability (Eq. 2 in Scheme 2).

On the other hand, it was also found that the hydrogenation catalyzed by Rh/Al_2O_3 in THF gave **5** more effectively than that in EtOH (entry 10 in Table 1). However, the yield was unsatisfactory due to a minor product, which seemed to result from overreduction (Eq. 3 in Scheme 2). When the reaction was carried out at 0 °C, the overreduction was avoided and the yield of **5** was improved. Further, shortening the reaction time suppressed the conversion of **5** to **6**, and a better result was obtained for 40 min than for 60 min. Additionally, EtOAc proved to be a better solvent for this hydrogenation reaction than EtOH, THF, dioxane, DME, and

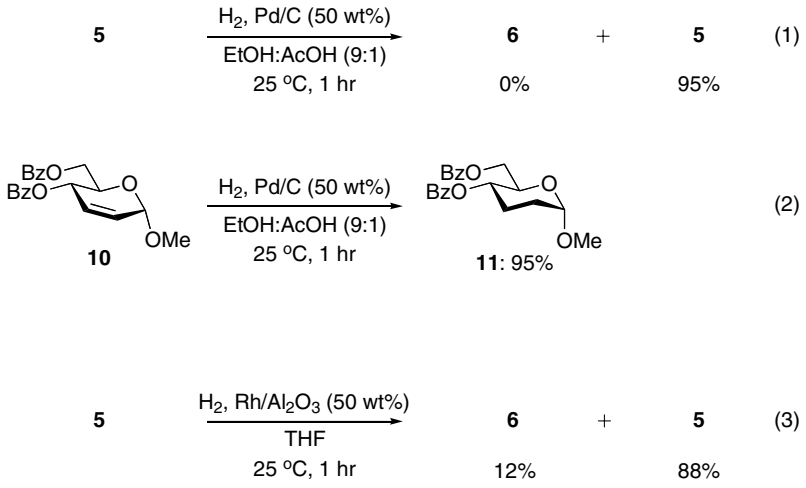
Table 1. Hydrogenations of **4** under several conditions



Entry	Catalyst	Amount of catalyst (wt %)	Solvent	Temperature (°C)	Time (min)	Yield[a] (%)	
						5	**6**
1	Pd/C	50	EtOH	25	60	14	78
2[b]	$Pd(OH)_2/C$	50	EtOH	25	60	17	76
3	Pt/C	50	EtOH	25	60	4	63
4[c]	Raney-Ni	50	EtOH	25	60	18	44
5	Rh/Al_2O_3	50	EtOH	25	60	50	39
6	Pd/C	50	THF	25	60	37	59
7	Pd/C	50	EtOAc	25	60	35	61
8[d]	Pd/C	50	MeOH	25	60	10	78
9	Pd/C	50	EtOH/AcOH (9/1)	25	60	13	80
10	Rh/Al_2O_3	50	THF	25	60	58	17
11	Rh/Al_2O_3	50	THF	0	40	66	23
12	Rh/Al_2O_3	50	Dioxane	10	40	69	24
13	Rh/Al_2O_3	50	DME	0	40	69	26
14	Rh/Al_2O_3	50	Acetone	0	40	71	27
15	Rh/Al_2O_3	50	EtOAc	0	40	77	21
16	Rh/Al_2O_3	10	EtOAc	0	60	83	17
17	Rh/Al_2O_3	10	EtOAc/toluene (9/1)	0	60	86	14



[a] Isolated yield.
[b] Ethyl glycoside **7** was produced in 4% yield.
[c] 10% of **4** was recovered, and **8** was produced in 21% yield.
[d] Methyl glycoside **9** was produced in 5% yield.

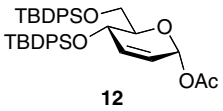
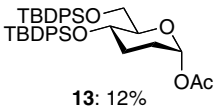
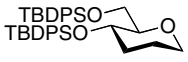
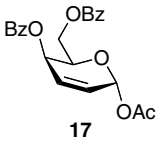
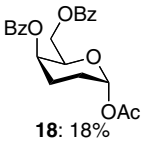
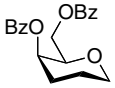
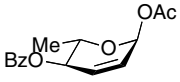
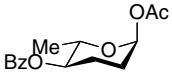


Scheme 2. Hydrogenations of **5** and **10**.

acetone. Pursuing milder conditions drives us to decrease the amount of the catalyst and add toluene. We should, therefore, conclude that the hydrogenation of hex-2-enopyranosyl acetate **4** using 10 wt % Rh/Al_2O_3 in EtOAc/toluene (9/1, v/v) at 0 °C for 1 h is the optimal condition for chemoselectively obtaining hexopyranosyl acetate **5** in high yield.

We next investigated the hydrogenation of several hex-2-enopyranosyl acetates under the two optimized conditions: condition A, using Pd/C (50 wt % to starting materials) in EtOH/AcOH (9/1, v/v) at 25 °C; and condition B, using Rh/Al_2O_3 (10 wt % to starting materials) in EtOAc/toluene (9/1, v/v) at 0 °C. These results are summarized in Table 2. The D-*erythro* acetates having Ac or TBDPS group as protecting groups, **1** and **12**, underwent chemoselective reduction, providing the corresponding hexopyranosyl acetates **3** or **14** under condition A, and the corresponding 2,3-disubstituted tetrahydropyrans **2** or **13** under condition B, in good yield with good chemoselectivity, respectively. Furthermore, β-acetate **15** and D-*threo* acetate **17** were both also converted chemoselectively into two molecular hydrogen adducts **3** and **19** with good to high selectivities, and into one molecular hydrogen adduct **16** and **18** with excellent selectivities. To demonstrate the feasibility of the reduction of 6-deoxy sugar, the synthesis of **21** and **22** by hydrogenations of **20** was also investigated. The

Table 2. Chemoselective hydrogenations of several hex-2-enopyranosyl acetates

Entry	Starting material	Yield[a]		
		Conditions A[b]		Conditions B[c]
1	**1**	**2**: 12%	**3**: 77%	**2**: 93%, **3**: 0%
2	 **12**	 **13**: 12%	 **14**: 88%	**13**: 80%, **14**: 16%
3	 **15**	 **16**: 4%	**3**: 84%	**16**: 91%, **3**: 0%
4	 **17**	 **18**: 18%	 **19**: 72%	**18**: 89%, **19**: 0%
5	 **20**	 **21**: 15%	 **22**: 73%	**21**: 84%, **22**: 4%

[a] Isolated yield.
[b] Pd/C (50 wt % to starting materials) in EtOH/AcOH (9/1, v/v) at 25 °C for 1 h.
[c] Rh/Al_2O_3 (10 wt % to starting materials) in EtOAc/toluene (9/1, v/v) at 0 °C for 1 h.

hydrogenation of **20** under condition A gave **22** in good yield, while that under condition B resulted in 84% yield of **21** with good chemoselectivity.

In conclusion, we demonstrated a novel chemoselective reduction of hex-2-enopyranosyl acetates to selectively produce hexopyranosyl acetates or 2,3-disubstituted tetrahydropyrans, regardless of their configurations and substituents.

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