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Efficient Synthesis of Rare Sugar D-Allal via Reversal of Diastereoselection in the Reduction of Protected 1,5-Anhydrohex-1-en-3-uloses: Protecting Group Dependence of the Stereoselection

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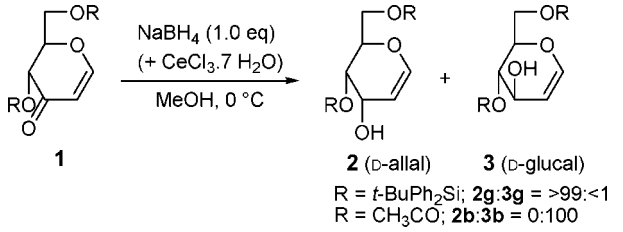
Received July 31, 2008

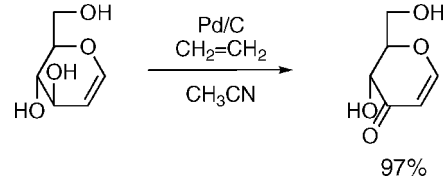


D-Allal was selectively obtained by reducing bulky-silyl-protected 1,5-anhydrohex-1-en-3-uloses using the $NaBH_4$—$CeCl_3 \cdot 7H_2O$ system. The crucial point of this synthesis is the nature of the protecting group. When bulky silyl group such as *t*-butyldiphenylsilyl was used as substrate, protected D-allal was obtained in >99% selectivity. In contrast, when acetylated enone was used, protected D-glucal was obtained exclusively. The addition of $CeCl_3 \cdot 7H_2O$ was also found to influence selectivity.

Rare sugars have received much attention from the viewpoint of biological activity, such as their ability to act as inhibitors of various glycosidases.[1] However, in spite of their potential importance in medicine and pharmacy, studies of their biological effects are limited because of low natural abundance and difficulty in synthesis. In the synthesis of D-allose, an enzymatic method[2] and several chemical methods have been reported. As examples of the chemical method, Humoller reported in 1962 a method starting from D-ribose using cyanohydrins,[3] while Baker et al. reported the reduction of 1,2,5,6-di-*O*-isopropylidene-α-D-ribo-hexofuranos-3-ulose hydrate.[4] Those methods generally require many steps and relatively expensive starting materials. Therefore, the development of a simple and efficient method has been much awaited. Several methods have been reported for the synthesis of protected D-allal, a glycal type of D-allose.[5] However, to our knowledge, there are only a handful of reports of the efficient synthesis of D-allal. Danishefsky's method involves the stereospecific oxygenation at C-3 of tri-*O*-acetyl-D-glucal-derived sulfoxides in a [2,3]-sigmatropic rearrangement, followed by base-catalyzed acetyl migration from *O*-4 to *O*-3.[6] Diaz and Castillon recently reported a synthetic route to allal and glucal derivatives, which is based on a sequential process involving olefination-cyclization-elimination, using pentoses as starting material.[7] Danishefsky and co-workers reported oligosaccharide synthesis based on glycosidation using glycal as glycosyl donor/acceptor.[8] Therefore, the development of an efficient method for the synthesis of D-allose is also important from the viewpoint of the synthesis of oligosaccharides containing a rare sugar. We describe in this communication the facile synthesis of D-allal based on the chemo- and diastereoselective reduction of protected 1,5-anhydrohex-1-en-3-uloses.

In 1999, we were the first to report a Pd/C—ethylene system for the oxidation of benzylic and allylic alcohols to corresponding ketones.[9] A representative example of this reaction is shown below. Treatment of D-glucal (1,5-anhydro-2-deoxy-D-*arabino*-hex-1-enitol) with a catalytic amount of Pd/C under hydrogen atmosphere in ethanol gave "normal" hydrogenated 2-deoxy-1,5-anhydroglucitol (D-*r*-2-hydroxymethyl-tetrahydropyran-*t*-3, *c*-4-diol) in 92% yield. In contrast, when the same reaction was employed under ethylene atmosphere, dehydrogenated 1,5-anhydro-2-deoxy-D-*erythro*-hex-1-en-3-ulose was obtained in 97% yield (Scheme 1).[10] It should be mentioned that the reaction under argon atmosphere gave hydrogenated and dehydrogenated products in almost the same ratio.

SCHEME 1. Treatment of D-Glucal with a Catalytic Amount of Pd/C under Ethylene Atmosphere



Our strategy for the preparation of D-allal is to reduce the carbonyl moiety of 1,5-anhydrohex-1-en-3-ulose that can be easily obtained according to the above method in a chemoselective and stereoselective manner. If the hydride attack takes place from the β-face of the carbonyl group, D-allal will be obtained efficiently (Scheme 2).

After examining various reducing agents and reaction conditions, we found that D-allal type **2** was obtained predominantly by reducing silyl-protected 1,5-anhydrohex-1-en-3-uloses using

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(5) For the synthesis of benzylidene D-allal: (a) Kaluza, Z.; Chmielewski, M. *Tetrahedron* **1989**, *45*, 7195–7200. (b) Sharma, M.; Brown, R. K. *Can. J. Chem.* **1966**, *44*, 2825–2835. (c) Godage, H. Y.; Fairbanks, A. J. *Tetrahedron Lett.* **2003**, *44*, 3631–3635. For the synthesis of D-allal: (d) Guthrie, R. D.; Irvine, R. W. *Carbohydr. Res.* **1979**, *72*, 285–288.

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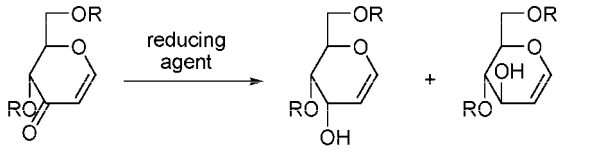
10.1021/jo801596q CCC: $40.75 © 2008 American Chemical Society
Published on Web 10/14/2008

SCHEME 2. Chemoselective and Stereoselective Reduction of 1,5-Anhydrohex-1-en-3-ulose



R = H (**1a**), MeCO (**1b**), Me_3CCO (**1c**) PhCO (**1d**), *t*-$BuMe_2Si$ (**1e**) *i*-Pr_3Si (**1f**), *t*-$BuPh_2Si$ (**1g**)

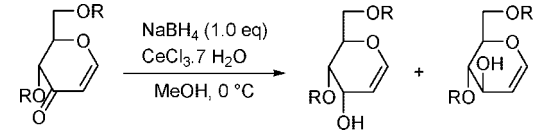
protected D-allal (**2a**—**2g**)

protected D-glucal (**3a**—**3g**)

the $NaBH_4$−$CeCl_3 \cdot 7H_2O$ system[11] (method A). As shown in Table 1, when *t*-butyldimethylsilyl ether of 1,5-anhydrohex-1-en-3-ulose was employed under the conditions for method A, the ratio of the reduction product, that is, protected D-allal type (**2**):protected D-glucal type (**3**), was 77:23 (entry 9). In contrast, in the case of acetylated 1,5-anhydrohex-1-en-3-ulose, the ratio of protected (**2**):protected (**3**) was 0:100 (method B, entry 4). Encouraged by these reversal results, we examined the nature of the silyl group. We changed the silyl group to a more bulky group and found that when bulky silyl groups such as triisopropylsilyl and *t*-butyldiphenylsilyl were used, the ratio of D-allal type (**2**) increased to afford protected D-allal type in >99% selectivity (entry 13). The addition of $CeCl_3 \cdot 7H_2O$ was also found to influence the direction of the hydride attack. For example, even when triisopropylsilyl ether and *t*-butyldiphenylsilyl ether were used, the ratios of **2**:**3** decreased to 94:6 and 91:9, respectively, in the absence of $CeCl_3 \cdot 7H_2O$ (method A, entries 12 and 14), and the chemical yields were also low. When *t*-butyldimethylsilyl ether was used, the ratio of **2**:**3** was reversed from 77:23 (method A, entry 9) to 22:78 (method B, entry 10). On the other hand, in the case of acylated 1,5-anhydrohex-1-en-3-uloses, method B always afforded glucal type **3** in high selectivity (R = acetyl, **2b**:**3b** = 0:100; R = benzoyl, **2d**:**3d** = 5:95; R = pivaloyl, **2c**:**3c** = 7:93).[10] It should be mentioned that when unprotected 1,5-anhydrohex-1-en-3-ulose was treated with a combination of $NaBH_4$ and $CeCl_3 \cdot 7H_2O$, glucal type **3** was obtained predominantly (method A, 23:77; method B, 3:97), although the chemical yield was moderate or low (53 and 21%, respectively, entries 1 and 2).

The isolated yield was determined after reduction by silica gel column chromatography. The ratio of **2** to **3** was determined by ^{1}H NMR analysis after desilylation and peracetylation in the case of silylated substrates, whereas in the case of acylated substrates, deacylation (if necessary) and peracetylation were performed to estimate the ratio correctly by derivatizing to 3-epimers of peracetylated products.

TABLE 1. Reduction of 4,6-Diprotected 1,5-Anhydro-2-deoxy-D-erythro-hex-1-en-3-uloses



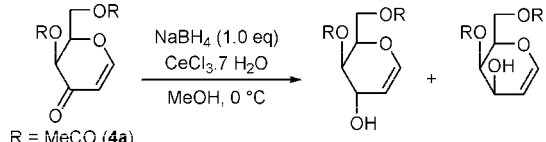
1a—1g **2a—2g** **3a—3g**

entry	R	method[a]	time/h	yield/%[b]	ratio[c] **2**:**3**
1	H	A	1	53	23:77
2	H	B	1	21	3:97
3	MeCO	A	1	73	22:78
4	MeCO	B	1	61	0:100
5	Me_3CCO	A	5	67	69:31
6	Me_3CCO	B	1	62	7:93
7	PhCO	A	4	71	42:58
8	PhCO	B	1	58	5:95
9	*t*-$BuMe_2Si$	A	4	64	77:23
10	*t*-$BuMe_2Si$	B	4	41	22:78
11	*i*-Pr_3Si	A	5	76	98:2
12	*i*-Pr_3Si	B	2	23	94:6
13	*t*-$BuPh_2Si$	A	5	82	>99:1<
14	*t*-$BuPh_2Si$	B	2	18	91:9

[a] Method A: 1.0 equiv of $CeCl_3 \cdot 7H_2O$ was added. Method B: $CeCl_3 \cdot 7\ H_2O$ was not added. [b] Isolated yield after silica gel column chromatography. [c] Ratio was determined by ^{1}H NMR analysis afer peracetylation of a crude mixture.

In the case of protected D-galactal (1,5-anhydro-2-deoxy-D-*threo*-hex-1-en-3-ulose), the protecting group did not have a marked effect on stereoselectivity, as shown in Table 2. Regardless of the nature of the protecting group at 4 and 6 positions, galactal type **6** was obtained.[10]

TABLE 2. Reduction of 4,6-Diprotected 1,5-Anhydro-2-deoxy-D-threo-hex-1-en-3-uloses



R = MeCO (**4a**), *t*-$BuPh_2Si$ (**4b**)

5a, 5b **6a, 6b**

entry	R	method[a]	time/h	yield/%[b]	ratio[c] **5**:**6**
1	CH_3CO	A	1	77	2:98
2	CH_3CO	B	1	58	0:100
3	*t*-$BuPh_2Si$	A	4	79	5:95
4	*t*-$BuPh_2Si$	B	3	63	0:100

[a] Method A: 1.0 equiv of $CeCl_3 \cdot 7\ H_2O$ was added. Method B: $CeCl_3 \cdot 7\ H_2O$ was not added. [b] Isolated yield after silica gel column chromatography. [c] Determined by ^{1}H NMR analysis afer peracetylation of a crude mixture.

As for reaction mechanism, the conformation of substrate enone should be important for consideration of stereoselective reduction, especially to explain the effect of protecting groups and reducing agents on stereoselectivity, steric environment at 3-position should affect the course of stereoselective reduction. The detailed study is now ongoing.

In summary, $NaBH_4$ reduction in the presence of 1 equiv of $CeCl_3 \cdot 7H_2O$ (method A) and $NaBH_4$ reduction in the absence of 1 equiv of $CeCl_3 \cdot 7H_2O$ (method B) of 4,6-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*erythro*-hex-1-en-3-ulose and 4,6-di-*O*-diphenyl-*t*-butylsiloxy derivatives gave the glucal type and its 3-epimer allose derivative in >99% selectivity, respectively.

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Studies of oligosaccharide synthesis containing rare sugar allose are ongoing.

Experimental Section

All the reactions were performed under an argon atmosphere using Schlenk tubes techniques and used freshly distilled chemicals and solvents.

Typical Procedure for Reduction of 4,6-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-erythro-hex-1-en-3-ulose (entry 4 in Table 1). In a Schlenk tube were placed 4,6-di-*O*-acetyl-1,5-anhydro-2-deoxy-D-*erythro*-hex-1-en-3-ulose (114.1 mg, 0.5 mmol) and methanol (5 mL). A mixture was cooled to 0 °C, then $NaBH_4$ (19 mg, 0.5 mmol) was added slowly. The mixture was stirred at 0 °C for 1 h, after confirmation of the consumption of the starting material by TLC, the mixture was quenched with H_2O (1 mL). After allowing the reaction mixture to cool to room temperature, the precipitates were removed by filtration, and the filtrate was extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and evaporated to afford the crude product, which was purified by silica gel column chromatography using 3:1 mixture of hexane:ethyl acetate (3:1) to give the reduction product **3b** (R = MeCO) (71.4 mg, 61%). $[\alpha]_D$ = 59.9° (*c* 1.0, $CHCl_3$). IR (thin film): ν_{max} (cm^{-1}) 3467, 2960, 1744, 1650, 1598, 1372, 1238, 1141, 1097, 1045, 910, 815, 733, 603; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 3H), 2.14 (s, 3H), 2.48 (br s, 1H), 4.11−4.15 (m, 1H), 4.2−4.4 (m, 3H), 4.8−4.9 (m, 1H), 4.96 (dd, *J* = 2.4, 6.8 Hz 1H), 6.40 (dd, *J* = 1.2, 6.4 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 20.6, 20.8, 61.9, 67.1, 71.6, 73.9, 102.85, 102.88, 144.0, 144.2.

Typical Procedure for Reduction of 4,6-di-*O*-*t*-butyldiphenylsilyl-1,5-anhydro-2-deoxy-D-erythro-hex-1-en-3-ulose (entry 13 in Table 1). In a Schlenk tube were placed 4,6-di-*O*-*t*-butyldiphenylsilyl-1,5-anhydro-2-deoxy-D-*erythro*-hex-1-en-3-ulose (1.86 g, 3.0 mmol), $CeCl_3 \cdot 7H_2O$ (1.12 g, 3.0 mmol), and methanol (25 mL). A mixture was cooled to 0 °C, then $NaBH_4$ (113.5 mg, 3.0 mmol) was added slowly. The mixture was stirred at 0 °C for 4 h; after confirmation of the consumption of the starting material by TLC, the mixture was quenched with H_2O (5 mL). After allowing the reaction mixture to cool to room temperature, the precipitates were removed by filtration, and the filtrate was extracted with ethyl acetate (15 mL × 3). The combined organic layers were dried over anhydrous magnesium sulfate, filtered, and evaporated to afford the crude product, which was purified by silica gel column chromatography using 40:1 mixture of hexane:ethyl acetate to give the reduction product **2g** (R = *t*-$BuPh_2Si$) (1.5 g, 80%) $[\alpha]_D$ = 42.9° (*c* 1.0, $CHCl_3$). IR (thin film): ν_{max} (cm^{-1}) 3559, 3070, 2930, 2857, 1960, 1892, 1645, 1464, 1429, 1112, 998, 822, 699; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.98 (s, 9H), 1.00 (s, 9H), 2.1 (br s, 1H), 3.5−3.6 (m, 1H), 3.80 (q, *J* = 4.0 Hz, 1H), 3.87 (dd, *J* = 3.2, 8.0 Hz, 1H), 3.9−4.0 (m, 1H),4.1−4.2 (m, 1H) 7.2−7.4 (m, 11H), 7.5−7.6 (m, 8H), 7.7−7.8 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 19.3, 19.4, 26.6, 26.9, 27.0, 62.2, 63.5, 69.6, 75.1, 100.0, 127.55, 127.58, 127.7, 127.8, 128.0, 128.3, 129.5, 129.59, 129.64, 130.1, 130.2, 132.7, 133.0, 133.5, 133.6, 134.8, 135.6, 135.7, 135.76, 135.84, 145.7; MS (ESI) *m*/*z*: 624 ($M + H^+$) For determination of **2/3** ratio, small part of crude product was desilylated with *n*-Bu_4NF and then peracetylation for ^{1}H NMR analysis.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" and No. B17340020 from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

Supporting Information Available: Experimental procedures and spectra data for important compounds including new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO801596Q