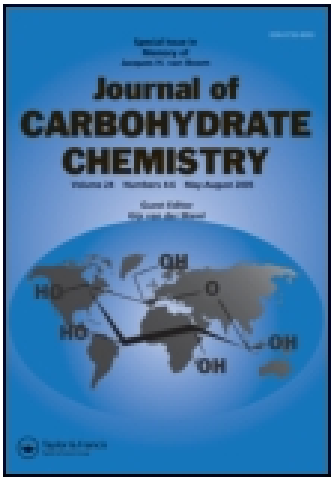

Journal of Carbohydrate Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lcar20

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Published online: 16 Aug 2006.

To cite this article: Brent Mann , Daniel Pitts & Jennifer Koviach (2005) Synthesis of α-2-Deoxyglycosides by Acid-Mediated Conjugate Addition, Journal of Carbohydrate Chemistry, 24:2, 161-168, DOI: 10.1081/CAR-200059931

To link to this article: http://dx.doi.org/10.1081/CAR-200059931

Journal of Carbohydrate Chemistry, 24:161–168, 2005

ISSN: 0732-8303 print
DOI: 10.1081/CAR-200059931

Synthesis of α-2-Deoxyglycosides by Acid-Mediated Conjugate Addition

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A new method for the synthesis of α-2-deoxyglycosides from hex-1-en-3-uloses is reported. Several acids were surveyed for their ability to mediate the conjugate addition of cyclohexanol to a glucal derived α,β-unsaturated ketone. Although several acids successfully afforded the α-2-deoxy-3-uloside as a single anomer, $Ph_3P \cdot HBr$ in benzene afforded the highest yield of product. These conditions were then applied to other alcohol nucleophiles, and it was found that nonsterically hindered alcohols readily undergo conjugate addition. Finally, the stereoselectivity of reduction of the resulting α-2-deoxy-3-uloside was determined for several hydride-reducing agents.

Keywords 2-Deoxyglycosides, Conjugate addition

INTRODUCTION

Many antibiotic and antitumor natural products contain one or more 2-deoxyglycosides.[1] Although the aglycon is typically responsible for the biological activity, the carbohydrate moieties are necessary in many cases for the bioactivity of the drug.[2] Since many 2-deoxy sugars are not readily isolated from nature, it is important that we have access to the preparation of such compounds. Many 2-deoxyglycosides also contain unusual stereochemistry or functionality at C-3, including *O*-alkylation, branching, amines, and nitro groups. Many of these functionalities could be installed from ketones such as **2** (Sch. 1).[3–6] We envisioned that ketone **2** could be readily prepared by conjugate addition of nucleophilic alcohols to hex-1-en-3-uloses, such as **1**

Received November 29, 2004; accepted January 1, 2005.
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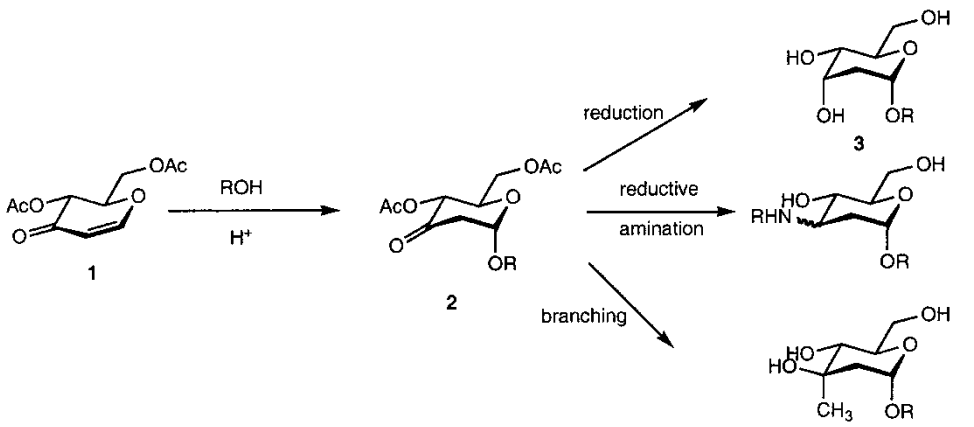


Scheme 1: Synthesis of 2-deoxyglycosides by conjugate addition followed by functionalization.

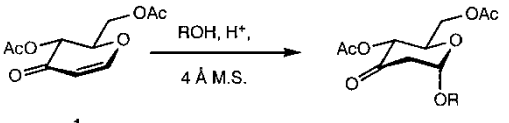
(Sch. 1). There are several previous reports of conjugate addition of alcohols to hex-1-en-3-uloses under basic conditions, but the reported yields are typically low, unless the nucleophile is the solvent, such as methanol.[7] We report here our studies on the acid-mediated conjugate addition of alcohols to the hex-1-en-3-ulose **1**, derived from D-glucal, as well as the stereoselectivity of reduction by several hydride reagents to give compound **3**.

RESULTS AND DISCUSSION

Compound **1** was prepared from 3,4,6-tri-*O*-acetyl-D-glucal either by direct oxidation with *in situ* generated Koser's reagent[8] or by a three-step procedure involving (1) global deacetylation, (2) selective allylic oxidation with pyridinium dichromate, and (3) acetylation.[9]

We first surveyed a series of acids in several solvents for the conjugate addition of cyclohexanol to **1** (entries 1–5, Table 1). Very mild acids such as pyridinium *p*-toluenesulfonic acid (PPTS) resulted in no conjugate addition. However, stoichiometric amounts of acids, such as *p*-toluenesulfonic acid, camphorsulfonic acid, and $Ph_3P \cdot HBr$, afforded exclusively the α-cyclohexyl glycoside. The stereoselectivity most likely arises due to the reversibility of the conjugate addition, resulting in the most stable glycoside. Nonpolar solvents (CH_2Cl_2 and benzene) were found to be superior to polar solvents (CH_3CN and THF), which were either sluggish or resulted in decomposition of starting material. The optimal conditions were found to be $PPh_3 \cdot HBr$ in benzene in the presence of 4 Å molecular sieves, which afforded a 61% yield of the cyclohexyl glycoside. Although the starting material is cleanly and completely converted into product as determined by monitoring by TLC and ^1H NMR, the product was found to be somewhat unstable and decomposed upon isolation and purification, resulting in lower yields than expected.

Table 1: Acid-mediated addition of alcohols to hex-1-en-3-ulose 1.



1 2

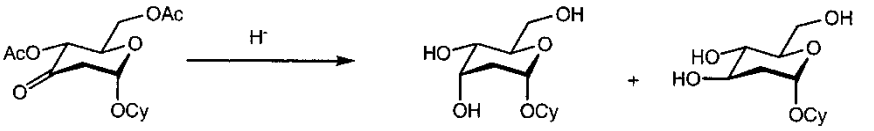
2a: R = cyclohexyl
2b: R = Bn
2c: R = 4-pentenyl
2d: R= 1,2:3,4-di-o-isopropylidene-D-galactose

Entry	Nucleophile	Acid	Solvent	Product	Yield
1	CyOH (1.5 eq.)	*p*-TsOH (1.0 eq.)	CH_2Cl_2	**2a**	52%
2	CyOH (1.5 eq.)	*p*-TsOH (1.0 eq.)	PhH	**2a**	38%
3	CyOH (1.5 eq.)	HBr · PPh_3 (1.0 eq.)	CH_2Cl_2	**2a**	N.R.
4	CyOH (2.5 eq.)	HBr · PPh_3 (1.5 eq.)	PhH	**2a**	61%
5	CyOH (1.5 eq.)	CSA (1.5 eq.)	PhH	**2a**	37%
6	BnOH (1.5 eq.)	HBr · PPh_3 (0.1 eq.)	PhH	**2b**	51%
7	4-penten-1-ol (1.5 eq.)	HBr · PPh_3 (0.5 eq.)	PhH	**2c**	62%
8	1,2:3,4-di-*O*-isopropylidene-D-galactose (1.5 eq.)	HBr · PPh_3 (1.0 eq.)	PhH	**2d**	40%
9	diacetone-D-glucose (1.5 eq.)	HBr · PPh_3 (2.0 eq.)	PhH	N.A.	N.R.
10	CBZ-Ser-OMe (2.0 eq.)	HBr · PPh_3 (0.5 eq.)	PhH	N.A.	N.R.

We then investigated the use of other alcohols as nucleophiles using our optimal conditions (entries 6–10, Table 1). Nonsterically hindered alcohols such as benzyl alcohol and 4-penten-1-ol cleanly afforded exclusively the α-anomers with catalytic $Ph_3P \cdot HBr$. The yield was reduced when the more sterically hindered 1,2:3,4-di-*O*-isopropylidene-D-galactose was utilized as the nucleophile, and no product was observed with diacetone-D-glucose, even under forcing conditions using excess acid and heat. In addition, as expected, alcohols prone to acid-catalyzed elimination, such as *N*-CBZ-serine-OMe, were not useful as nucleophiles.

With the hex-1-en-3-ulose **2a** in hand, we investigated the stereoselectivity of hydride reduction of the ketone to an alcohol, and these results are shown in Table 2. Previous studies have shown that simple $NaBH_4$ reduction of **2b** affords the *allo* isomer **3**, while Luche reduction results in the *gluco* isomer **4**, which we verified.[7b] We found that $NaBH_4$ and DIBAL-H afforded the *allo* isomer as the major product, while L-Selectride was completely selective for the *allo* isomer. Reduction with $LiAlH_4$ was not selective, affording both **3** and **4** almost equally. Because compound **2a** is somewhat unstable to purification by silica gel chromatography, we attempted a $NaBH_4$ reduction of crude **2a**. However, this sequence did not result in a higher overall yield, affording **3**/**4** in 56% yield from **1**.

Table 2: Hydride reduction of 2a.



2a 3 4

Entry	Conditions	Yield	3:4
1	1. $NaBH_4$; Amberlite IRN-78 $^-$OH form, MeOH	85%	6:1
2	DIBAL-H, CH_2Cl_2	63%	7.7:1
3	L-Selectride	50%	25:1
4	$LiAlH_4$	77%	1.6:1

CONCLUSIONS

We have developed a two-step method for the synthesis of 2-deoxyglycosides from hex-1-en-3-uloses derived from glucal. The reaction is most useful when nonsterically hindered alcohols that are not subject to elimination are utilized as the nucleophile. Hydride reduction of the resulting ketone typically affords a mixture of the *allo* and *gluco* isomers, though the *allo* glycoside can be prepared almost exclusively by reduction with L-Selectride.

EXPERIMENTAL

General Methods

All reactions were performed under Ar in oven-dried glassware with anhydrous solvent. Melting points were obtained on a Mel-Temp apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker spectrometer at 400 MHz and 100 MHz for ^{1}H and ^{13}C, respectively. Elemental analyses were performed by Prevalere Life Sciences. TLC was performed on Merck 60 F_{254} plates with 1:1 hexanes/ethyl acetate as eluent, and visualized first by UV light and second by anisaldehyde stain. Column chromatography was performed using silica gel 60 Å 32–63 μm purchased from Sorbent Technologies.

*General procedure for the preparation of 2a–d: Cylcohexyl-4,6-di-O-acetyl-2-deoxy-α-D-erythro-hexopyranosid-3-ulose (**2a**)*

The enone **1** (139 mg, 0.609 mmol) was dissolved in benzene (6 mL) under Ar. Crushed 4 Å molecular sieves, $Ph_3P\cdot HBr$ (250 mg, 0.728 mmol) and cyclohexanol (0.16 mL, 1.5 mmol) were added, and the reaction was stirred at rt overnight, at which time TLC analysis indicated disappearance of starting

material. The reaction was concentrated to approximately 1/2 volume and then purified by pouring directly onto a silica gel column using hexane: ethyl acetate (2:1) as eluent to afford **2a** (121 mg, 0.369 mmol, 61%), which solidified on standing. m.p. 60–62°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.39 (d, $J = 4.5$ Hz, 1H), 5.17 (d, $J = 10.2$ Hz, 1H), 4.22–4.33 (m, 3H), 3.55 (m, 1H), 2.82 (dd, $J = 4.6$, 14.2 Hz, 1H), 2.58 (d, $J = 14.1$ Hz, 1H), 2.15 (s, 3H), 2.08 (s, 3H), 1.8 (m, 2H), 1.7 (m, 2H), 1.5 (m, 1H), 1.2–1.4 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 198.1, 170.6, 169.4, 96.5, 75.8, 73.2, 69.5, 62.7, 46.6, 33.1, 31.2, 25.5, 24.0, 23.8, 20.7, 20.4. Anal. Calcd for $C_{16}H_{24}O_7$: C, 58.52; H, 7.37. Found: C, 58.21; H, 7.20.

*Benzyl-4,6-di-O-acetyl-2-deoxy-α-D-erythro-hexopyranosid-3-ulose (**2b**)*

Processed as described above, using **1** (45 mg, 0.20 mmol), $Ph_3P\cdot HBr$ (6.8 mg, 0.020 mmol), and benzyl alcohol (0.062 mL, 0.60 mmol) to afford **2b** (34 mg, 0.10 mmol, 51%), which solidified on standing. m.p. 123–126°C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ7.29–7.38 (m, 5H), 5.33 (d, $J = 4.3$ Hz, 1H), 5.23 (d, $J = 10.3$ Hz, 1H), 4.62 (AB, $J = 12.1$, $\Delta\nu = 59.1$ Hz, 2H), 4.33 (dd, $J = 4.1$, 11.9 Hz, 1H), 4.2 (m, 2H), 2.85 (dd, $J = 4.6$, 14.4 Hz, 1H), 2.71 (d, $J = 14.2$ Hz, 1H), 2.17 (s, 3H), 2.12 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.7, 170.6, 169.4, 136.4, 128.6, 128.1, 128.0, 97.6, 73.0, 69.7, 69.5, 62.5, 46.0, 20.8, 20.4. Anal. Calcd for $C_{17}H_{20}O_7$: C, 60.71; H, 5.99. Found: C, 60.71; H, 5.91.

*(4-pentenyl)-4,6-di-O-acetyl-2-deoxy-α-D-erythro-hexopyranosid-3-ulose (**2c**)*

Processed as described above, using **1** (135 mg, 0.591 mmol), 4-penten-1-ol (0.092 mL, 0.89 mmol), and $Ph_3P\cdot HBr$ (102 mg, 0.297 mmol) to afford **2c** as a colorless oil (114 mg, 0.362 mmol, 62%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ5.76 (dddd, $J = 6.6$, 6.6, 10.3, 17.0 Hz, 1H), 5.23 (d, $J = 4.3$ Hz, 1H), 5.19 (d, $J = 10.4$ Hz, 1H), 5.00 (d, $J = 17.7$ Hz, 1H), 4.96 (d, $J = 10.5$ Hz, 1H), 4.33 (dd, $J = 4.4$, 12.2 Hz, 1H), 4.35 (d, $J = 12.6$ Hz, 1H), 4.20 (m, 1H), 3.65 (ddd, $J = 6.5$, 6.5, 9.7 Hz, 1H), 3.41 (ddd, $J = 6.4$, 6.5, 9.6 Hz, 1H), 2.83 (dd, $J = 4.5$, 14.3 Hz, 1H), 2.65 (d, $J = 14.2$ Hz, 1H), 2.17 (s, 3H), 2.08 (s, 3H), 2.0 (m, 2H), 1.65 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 197.8, 170.6, 169.4, 137.8, 115.2, 98.5, 73.0, 69.4, 67.3, 62.5, 46.2, 30.1, 28.3, 20.8, 20.5. Anal. Calcd for $C_{15}H_{22}O_7$: C, 57.32; H, 7.05. Found: C, 56.96; H, 7.38.

*(1,2:3,4-di-O-isopropylidene-D-galactosyl)-4,6-di-O-acetyl-2-deoxy-α-D-erythro-hexopyranosid-3-ulose (**2d**)*

Processed as described above, using **1** (43 mg, 0.19 mmol), 1,2:3,4-di-*O*-isopropylidene-D-galactose (73 mg, 0.28 mmol), and $Ph_3P\cdot HBr$ (64 mg, 0.19 mmol) to afford **2d** as a colorless oil (37 mg, 0.075 mmol, 40%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ5.48 (d, $J = 5.0$ Hz, 1H), 5.30 (d, $J = 4.3$ Hz, 1H), 5.22 (d, $J = 10.4$ Hz), 4.60 (dd, $J = 2.4$, 7.9 Hz, 1H), 4.38 (dd, $J = 4.1$, 12.0 Hz, 1H), 4.19–4.4.35 (m, 4H), 3.90 (td, $J = 1.7$, 6.4 Hz, 1H), 3.73 (ABX, $J_{ax} = 6.2$ Hz,

$J_{bx} = 6.7$ Hz, $J_{AB} = 10.2$ Hz, $\Delta\nu = 29.6$ Hz, 2H), 2.84 (ddd, $J = 0.8.\ 4.6, 14.4$ Hz, 1H), 2.69 (dd, $J = 0.8, 14.3$ Hz, 1H), 2.17 (s, 3H), 2.11 (s, 3H), 1.51 (s, 3H), 1.43 (s, 3H), 1.32 (s, 6H). Anal. Calcd for $C_{22}H_{32}O_{12}$: C, 54.09; H, 6.60. Found: C, 53.84; H, 6.87.

*$NaBH_4$ reduction of **2a***

To the ketone **2a** (110 mg, 0.335 mmol) in methanol (3 mL) was added $NaBH_4$ (6.3 mg, 0.34 mmol). The reaction was stirred for 3 hr, at which time TLC analysis indicated disappearance of starting material. The reaction was quenched with water and diluted with ethyl acetate. The layers were separated, and the organic layer was washed with brine. The combined aq. layers were extracted with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was redissolved in methanol (3 mL), and Amberlite IRN-78 $^-$OH form was added. The reaction was stirred for 2 hr, at which time TLC analysis indicated completion. The reaction was filtered through Celite and concentrated, to afford an inseparable 6:1 mixture of **3** and **4** (71 mg, 0.29 mmol, 85%), which was not purified further. **3**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.09 (d, $J = 3.3$ Hz, 1H), 4.0 (br s, 1H), 3.72–3.89 (m, 4H), 3.61 (m, 1H), 3.48 (dd, $J = 3.2, 10.1$ Hz, 1H), 2.9 (br s, 1H), 2.5 (br s, 1H), 2.12 (ddd, $J = 0.85, 3.3, 14.6$ Hz), 1.88 (dt, $J = 3.4, 14.6$ Hz, 1H), 1.8 (m, 1H), 1.70 (m, 1H), 1.24–1.51 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 94.8, 75.1, 68.7, 67.6, 67.5, 62.6, 35.2, 33.3, 31.0, 25.5, 24.0, 23.6. Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00. Found: C, 58.62; H, 8.62.

*DIBAL-H reduction of **2a***

The ketone **2a** (43 mg, 0.13 mmol) was dissolved in CH_2Cl_2 (1.2 mL) and cooled to 0°C. DIBAL-H (1.0 M in CH_2Cl_2, 0.52 mL, 0.52 mmol) was added, and the reaction was stirred for 5 min before warming to rt. The reaction was stirred for 2 hr, at which time TLC analysis indicated disappearance of starting material. The reaction was cooled to 0°C, and methanol followed by sodium potassium tartrate were added, and the reaction was stirred for 1 hr. The reaction was diluted with ethyl acetate, and the layers were separated. The organic layer was washed with brine and the combined aq. layers were extracted with ethyl acetate. The combined org. layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography using 1:1 hexanes/ethyl acetate as eluent to afford an inseparable 7.7:1 mixture of **3:4** (20 mg, 0.081 mmol, 63%).

*L-Selectride reduction of **2a***

The ketone **2a** (37 mg, 0.11 mmol) was dissolved in THF and cooled to 0°C. L-Selectride (1 M in THF, 0.5 mL, 0.5 mmol) was added, and the reaction was warmed to rt. The reaction was stirred for 6 hr, at which time TLC analysis indicated completion. The reaction was cooled to 0°C, and 3 M NaOH

(0.2 mL) followed by 30% H_2O_2 (0.1 mL) were added. The reaction was stirred for 1 hr at 0°C, and then warmed to rt. The solution was filtered through Celite with ethyl acetate, and the organic layer was washed with brine. The aq. layer was extracted with ethyl acetate, and the combined org. layers were dried over Na_2SO_4,, filtered, and concentrated to afford an inseparable 25:1 mixture of **3:4** (13.4 mg, 0.054 mmol, 50%).

*$LiAlH_4$ reduction of **2a***

The ketone **2a** (50 mg, 11.4 mmol) was dissolved in THF and cooled to 0°C. $LiAlH_4$ (23 mg, 0.61 mmol) was added, and the reaction was warmed to rt. The reaction was stirred for 4 hr at which time TLC analysis indicated completion. The reaction was cooled to 0°C, quenched with water (0.23 mL), 1 M NaOH (0.23 mL), and water (0.46 mL), and filtered through Celite with ethyl acetate. The filtrate was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by column chromatography using 1:1 hexanes/ethyl acetate as eluent to afford an inseparable 1.6:1 mixture of **3** and **4** (28.5 mg, 0.116 mmol, 77%).

ACKNOWLEDGEMENT

We gratefully acknowledge financial support for this project from Research Corporation in the form of a Cottrell College Science Award and a Bates College intramural grant supported by the Howard Hughes Research Institution. This work was greatly facilitated by a 400 MHz NMR spectrometer that was purchased partly with funds from an NSF Major Research Instrumentation Program Grant, CHE-0115579.

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