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Hydrodeamination of β-enamino ketones to 1,2-dideoxy-D-threo-3-hexulose via palladium

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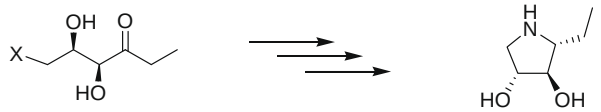
ABSTRACT

β-Enamino ketones were successfully synthesized in good to excellent yields by reaction of hex-1-en-3-uloses with amines. After hydrogenation on palladium catalyst, β-enamino ketones effectively underwent hydrodeamination and were converted to the corresponding 1,2-dideoxy-D-threo-3-hexulose derivatives in 89–95% yields.

1. Introduction

In 2007, Wong and co-workers reported the (2*R*,3*R*,4*R*)-2-(hydroxymethyl)pyrrolidine-3,4-diol compound **1** as quite specific and slightly more potent inhibitor of β-mannosidase.[1] (4*S*,5*R*)-6-Azido-4,5-dihydroxy-hexan-3-one (**2**)[1] and 1,2-dideoxy-D-threo-3-hexulose (**3**)[2] can be used as the precursors to prepare **1** (see Fig. 1). Herein, we report an efficient and convenient methodology to synthesize **3** from hex-1-en-3-ulose starting materials.

Hydrodeamination[3] was widely applied in the field of organic functional group transformation, including diazotization,[4] amination of the toluenesulfonamide,[5] nitrosation,[6] difluoroamine,[3b] and nucleophilic aromatic substitutions.[7] Many hydrodeaminations of benzylic amines, benzoyl amines, or primary amines have been investigated by catalytic hydrogenation, dissolving metal reduction,[8] or other reducing agents.[9] There have been a few directed hydrodeamination methods reported for the conversion of β-enamino ketones to ketones.[10] In this work, we reported the novel hydrodeamination of β-enamino ketones by hydrogenation on palladium catalyst to generate the corresponding 1,2-dideoxy-D-threo-3-hexulose products.



2. X = NH_2, **3.** X = OH

1

Figure 1.

2. Results and discussion

β-Enamino ketones **9–21** were prepared as the reference materials following the previous publication procedure via Michael addition of hex-1-en-3-uloses.[11] Hex-1-en-3-uloses **4–8** reacted with two equivalents of primary amines, including benzylamine, *n*-butylamine, and *n*-octylamine in MeOH for two hours to give the corresponding β-enamino ketones **9–21** in 80–96% yields (see Table 1).[11] The addition reactions were clean and smooth to give the high diastereoselective *Z*-geometry of the products due to the intramolecular hydrogen bonding.[12] All of β-enamino ketone structures were identified and determined by DEPT, NOESY, and other spectroscopic methods. For example, compound **10** possessed a characteristic broad singlet resonance at δ 10.11 for the amino proton, a doublet doublet resonance at δ 6.81 (J = 7.2, 13 Hz) for the alkene proton on C_1, and a doublet at δ 5.27 (J = 7.2 Hz) for the alkene proton on C_2.

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Table 1
The results of Michael addition of hex-1-en-3-uloses

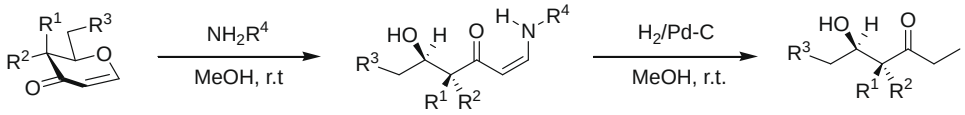
Hex-1-en-3-uloses (**4–8**)				β-Enamino ketones **9–21**		
Substrates	R^1	R^2	R^3	Compounds	R^4	Yields (%)
4	H	OMe	OMe	**9**	Bn	80
4	H	OMe	OMe	**10**	*n*-Bu	97
4	H	OMe	OMe	**11**	*n*-Oct	84
5	OMe	H	OMe	**12**	Bn	91
5	OMe	H	OMe	**13**	*n*-Bu	96
5	OMe	H	OMe	**14**	*n*-Oct	95
6	H	Isopropylidene		**15**	Bn	92
6	H	Isopropylidene		**16**	*n*-Bu	89
6	H	Isopropylidene		**17**	*n*-Oct	80
7	H	OBn	OBn	**18**	Bn	93
8	H	OBn	OBn	**19**	*n*-Bu	90
8	OBn	H	OBn	**20**	Bn	95
8	OBn	H	OBn	**21**	*n*-Bu	89

Palladium catalyst was commonly applied in the hydrogenation of organic compounds.[13] In the newly developed hydrodeamination, various β-enamino ketones **9–17** were treated with a catalytic amount of palladium in MeOH at room temperature for 4 h through the atmosphere by a hydrogen-filled balloon. After the reactions were complete, the normal work-up and purification with column chromatography on silica gel were performed. The desired 1,2-dideoxy-D-3-hexuloses were isolated in liquid form (**22–24**, see Scheme 1 and Table 2).

The benzylic group is one of the most popular protecting units for alcohol and carbohydrate compounds.[14] By applying the standard hydrodeamination procedure to benzyl-protected β-enamino ketones **18** and **19** (R^1 = H, R^2 = R^3 = OBn), the O-deprotected and hydrodeaminated 1,2-dideoxy-D-threo-3-hexulose **25** (R^1 = H, R^2 = R^3 = OH) was afforded in 89% and 93% yield, respectively. Furthermore, we performed the hydrodeamination to benzyl-protected β-enamino ketones **20** and **21**, in which the amino moiety was linked with Bn and *n*-Bu groups on nitrogen atom. The corresponding 1,2-dideoxy-D-erythro-3-hexulose **26** was produced in 89% and 95% yield, respectively, (see Scheme 2). Comparing benzyl-protected β-enamino ketones (**18–21**) with methyl-protected β-enamino ketones (**9–17**), we found that the benzyl-protected group was easily hydrogenated to hydroxyl group under the same reaction condition.

When we treated hex-1-en-3-uloses **5** with *N*,*N*-diethylamine (secondary amine) and acetamide by following the previous procedure, only the corresponding *N*,*N*-diethyl-β-enamino ketone **27** was obtained in 87% yield (see Scheme 3). We applied the same hydrodeamination to *N*,*N*-diethyl-β-enamino ketone **27**. The hydrogenated product **23** also succeeded in generating 90% yield.

We proposed a plausible mechanism for the hydrodeamination of β-enamino ketones **28** to 1,2-dideoxy-D-threo-3-hexulose **33** as shown in Scheme 4, which accounted for our approach and design. Palladium catalyst underwent hydrogenation toward β-enamino ketone **28** to give hydrido olefin palladium complex **29** and isomer



4-8 **9-21** **22-24**

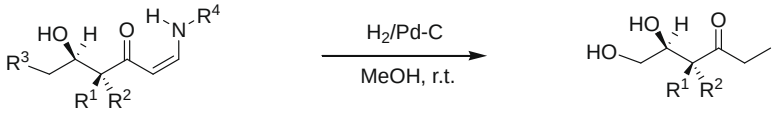
R^1 = H, OMe, OBn
R^2 = H, OMe, OBn, isopropylidene
R^3 = OMe, OBn, isopropylidene

R^4 = Bn, *n*-Bu, *n*-Oct

Scheme 1.

Table 2
The results of hydrodeamination of **β**-enamino ketones **9–17**

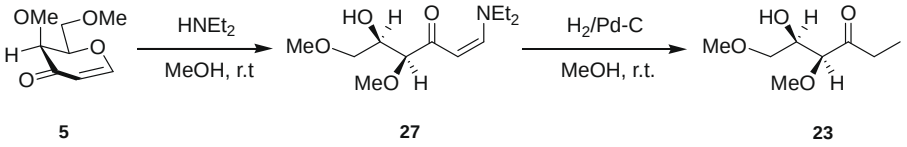
β-Enamino ketones **9–21**					1,2-Dideoxy-D-threo-3-hexuloses **22–24**	
Substrates	R^1	R^2	R^3	R^4	Compounds	Yields (%)
9	H	OMe	OMe	Bn	**22**	95
10	H	OMe	OMe	*n*-Bu	**22**	92
11	H	OMe	OMe	*n*-Oct	**22**	94
12	OMe	H	OMe	Bn	**23**	90
13	OMe	H	OMe	*n*-Bu	**23**	96
14	OMe	H	OMe	*n*-Oct	**23**	89
15	H	Isopropylidene		Bn	**24**	93
16	H	Isopropylidene		*n*-Bu	**24**	92
17	H	Isopropylidene		*n*-Oct	**24**	90



18. R^1 = H, R^2 = R^3 = OBn, R^4 = Bn
19. R^1 = H, R^2 = R^3 = OBn, R^4 = *n*-Bu
20. R^1 = R^3 = OBn, R^2 = H, R^4 = Bn
21. R^1 = R^3 = OBn, R^2 = H, R^4 = *n*-Bu

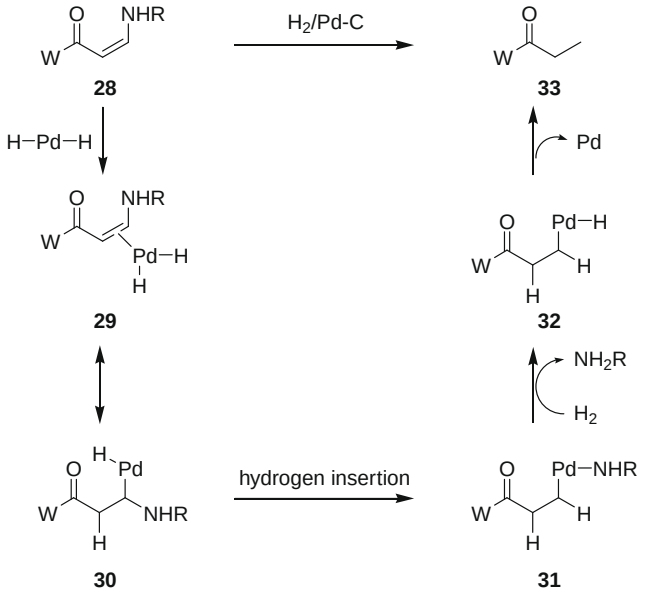
25. R^1 = H, R^2 = OH
26. R^1 = OH, R^2 = H

Scheme 2.



5 27 23

Scheme 3.



Scheme 4.

30.[15] The intramolecular hydrogen insertion took place to give aminopalladation adduct **31**.[15] After further hydrogenation, the intermediate **32** and by-product amine (NH_2R) were generated. In a control experiment for the hydrodeamination, we were able to identify the resultant amine (NH_2R) as a by-product by GC–mass spectroscopic technique. Finally, hydrogenation of intermediate **32** gave the target 1,2-dideoxy-D-threo-3-hexulose **33**.

In conclusion, β-enamino ketones were prepared as the starting materials by Michael addition of hex-1-en-3-uloses with primary amines. They underwent the novel hydrodeamination with a catalytic amount of palladium under hydrogen atmosphere to give 1,2-dideoxy-D-threo-3-hexuloses in excellent yields (89–93%).

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.06.112.

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