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Intramolecular Direct Aldol Reactions of Sugar Diketones: Syntheses of Valiolamine and Validoxylamine G

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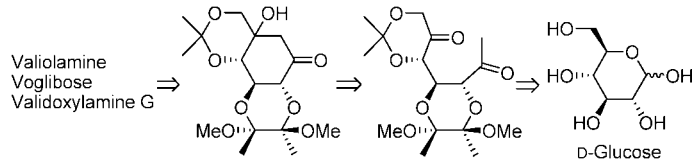
ABSTRACT



A new and stereoselective intramolecular direct aldol reaction of diketones derived from carbohydrates has been developed to construct carbocycles with D-*gluco*-, D-*galacto*-, D-*manno*-, and L-*ido*-configurations. The stereochemical outcome of the aldol reaction of the diketone is dependent on the base used. Transformation of D-*gluco*-aldols readily affords valiolamine which also constitutes a formal synthesis of voglibose. Facile conversion of D-*gluco*-cyclohexanones into validoxylamine G has been achieved in 12 steps with 15.1% overall yield from D-glucose.

The direct aldol reaction is one of the most concise and efficient carbon−carbon bond-forming reactions in the arsenal of synthetic chemists.[1] Direct aldol reactions catalyzed by L-proline and its derivatives have become a rapidly expanding area in contemporary organic synthesis during the past years.[2] Recently, DBU and DIPEA have been demonstrated to promote intermolecular direct aldol reactions.[3] These results have prompted us to disclose our efforts in the intramolecular variant of the direct aldol reactions which were employed to construct hydroxylated carbocycles from carbohydrates, a long-standing theme of our research program.[4]

Our endeavors in carba-aminodisaccharide synthesis have produced valienamine and 2-*epi*-valienamine containing pseudo-1,1′-*N*-linked disaccharides on the basis of transformation from quinic acid.[5] As a continuation of our efforts targeting pseudoamino oligosaccharides for biological evaluation, an efficient entry for hydroxylated carbocycles is required to transform them into primary carba-monosaccharide units with D-*gluco*-, D-*galacto*-, and D-*manno*-configurations.

In this paper, we describe facile construction of carbocycles via an intramolecular direct aldol reaction of diketones derived from carbohydrates and the transformation of the cyclized D-*gluco*-aldols into α-D-glucosidase inhibitors valiolamine (**5**), voglibose (**6**), and validoxylamine G (**7**).

Orally active antidiabetic medicine voglibose (**6**) (code: AO-128) is a *N*-substituted glycerol derivative of valiolamine (**5**)[6] and has attracted considerable interest due to its excellent inhibitory activity against α-D-glucosidases and its action

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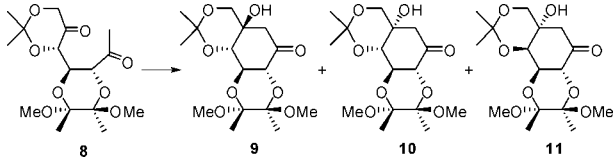
against disorders caused by hyperglycemia.[7] Validoxylamine G (**7**), a pseudoaminodisaccharide possessing valienamine (**4**) and valiolamine (**5**),[8] was found to be a very potent α-D-glucosidase inhibitor among the validamycin complexes.[9] Two syntheses of validoxylamine G (**7**) have been addressed with inefficient installation of the amine linkage; as a result, the overall yields were only 0.11 and 1.56% from optically resolved Diels−Alder *endo*-adduct[10] and D-glucose,[11] respectively, which hampered large scale production of **7** for further biological studies.

First, the formation of carbocycles (aldols) from D-glucose is shown in Table 1. It is noteworthy that L-proline-catalyzed

Table 1. Aldol-Cyclization Conditions of Diketone **8**

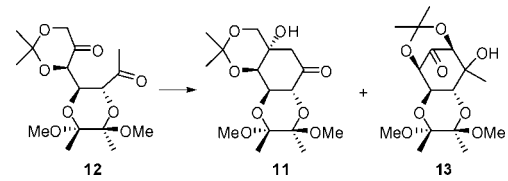


		results		
entry	conditions	**9**	**10**	**11**
1	L-Proline (0.3 equiv), DMSO	82%	8%	2%
2	(D)-Proline (0.3 equiv), DMSO	–	–	52%
3	Et_3N (1.5 equiv), CH_2Cl_2	–	–	95%
4	DIPEA (1.5 equiv), CH_2Cl_2	–	–	94%
5	LDA (1 equiv), Toluene, −78 °C	–	42%	–
6	NaHMDS (1 equiv), Toluene, −78 °C	–	62%	–
7	KHMDS (1 equiv), Toluene, −78 °C	–	75%	–

the direct aldol reaction of diketone **8**[12] (prepared from D-glucose in 6 steps with 30.8% overall yield) to give three cyclohexanones regioselectively, and L-*ido*-aldol **9** was isolated as the major carbocycle (entry 1). The structures of **9** and **11** were confirmed by X-ray crystallography, and the constitution of **10** was confirmed by conversion into known **5**. D-Proline only provided epimerized compound **11** in 52% yield (entry 2). It is surprising that amine bases, Et_3N and DIPEA, effected cyclization to give C-4 epimerized aldol **11** exclusively (entries 3−4). Among the strong bases used (entries 5−7), KHMDS gave the best yield of a very useful synthetic intermediate **10** stereospecifically, with the tertiary alcohol oriented at the α-face. The elaboration of **9** and **10** into valiolamine (**5**), voglibose (**6**), and validoxylamine G (**7**) will be addressed later in this paper.

Diketone **12**[13] (prepared from D-galactose in 6 steps with 29.8% overall yield) was subjected to different carbocyclization conditions to give a D-*galacto*-cyclohexanone **11**, and the results are shown in Table 2. L-Proline-catalyzed

Table 2. Aldol-Cyclization Conditions of Diketone **12**

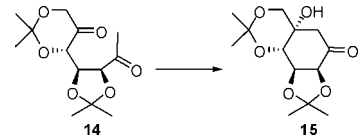


		results	
entry	conditions	**11**	**13**
1	(L)-Proline (0.3 equiv), DMSO	92%	–
2	(D)-Proline (0.3 equiv), DMSO	67%	–
3	Et_3N (1.5 equiv), CH_2Cl_2	99%	–
4	DIPEA (1.5 equiv), CH_2Cl_2	96%	–
5	LDA (1 equiv), Toluene, −78 °C	34%	42%
6	NaHMDS (1 equiv), Toluene, −78 °C	36%	40%
7	KHMDS (1 equiv), Toluene, −78 °C	35%	37%

direct aldol reaction provided **11** in 92% yield, albeit the long reaction time of 12 days (entry 1). When D-proline was employed, the reaction also gave **11**, but in a lower 67% yield (entry 2). Fortunately, Et_3N gave **11** exclusively in an excellent yield within one day (entry 3). Strong bases afforded a mixture of aldols **11** and **13** in similar amounts (entries 5−7).

The aldol-cyclization was further extended to prepare a D-*manno*-carbocycle as shown in Table 3. L-Proline-catalyzed

Table 3. Aldol-Cyclization Conditions of Diketone **14**



entry	conditions	results
1	(L)-Proline (0.3 equiv), DMSO	60%
2	(D)-Proline (0.3 equiv), DMSO	decomposed
3	Et_3N (1.5 equiv), CH_2Cl_2	decomposed
4	DIPEA (1.5 equiv), CH_2Cl_2	decomposed
5	LDA (1 equiv), Toluene, −78 °C	decomposed
6	NaHMDS (1 equiv), Toluene, −78 °C	decomposed
7	KHMDS (1 equiv), Toluene, −78 °C	decomposed

direct aldolization of diketone **14**[13] (prepared from D-mannose in 5 steps with 40% overall yield) furnished cyclohexanone **15** as a single diastereomer in 60% yield (entry 1). However, the use of D-proline did not afford any aldol (entry 2). Both amines (entries 3−4) and strong bases (entries 5−7) only gave fruitless results.

With cyclohexanones **9** and **10** in hand, attention was directed to synthesize valiolamine (**5**) and its containing

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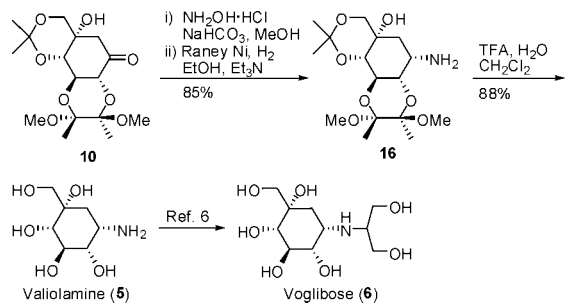
compounds. The cyclohexanone **10** was used to synthesize valiolamine (**5**) as they have four chiralities in common (Scheme 1). The remaining stereocenter was installed by a

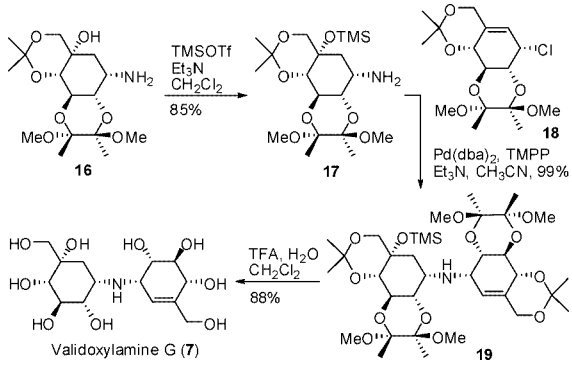
Scheme 1



reductive amination of **10** to give protected valiolamine **16**. After acid hydrolysis, the valiolamine (**5**) was obtained in 88% yield with specific rotation, ^{1}H and ^{13}C NMR spectral data in accord with the literature values.[14] Since voglibose (**6**) can be accessed by reacting valiolamine (**5**) with 1,3-dihydroxyacetone in the presence of $Na(CN)BH_3$,[6] the present synthesis of valiolamine (**5**) constitutes a formal synthesis of voglibose (**6**).

The amine **16** did not couple with allylic chloride **18**.[12] Hydrogen bonding with the tertiary alcohol might decrease the nucleophilicity of the amine in the coupling reaction (Scheme 2). Hence, the tertiary alcohol in **16** was protected

Scheme 2



as TMS-ether **17**. Palladium-catalyzed coupling[15] of **17** with chloride **18** smoothly gave blocked validoxylamine G **19** in an excellent yield. Acid hydrolysis then afforded validoxylamine G (**7**) in 88% yield. The specific rotation, ^{1}H and ^{13}C NMR spectral data are in good agreement with the reported values.[8,11]

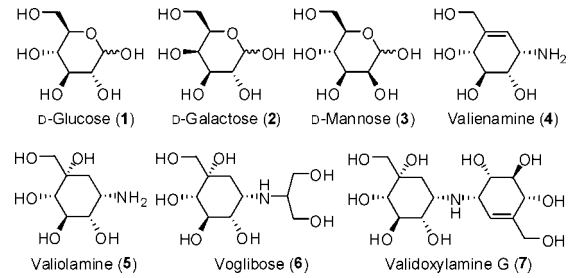


Figure 1. Structures of hexoses and α-D-glucosidase inhibitors **4**, **5**, **6**, and **7**.

In summary, we have developed the first intramolecular direct aldol reactions of diketones derived from carbohydrates, affording cyclohexanones with L-*ido*-, D-*gluco*-, D-*galacto*-, and D-*manno*-configurations. The diketone **8**, derived from D-glucose, gave either L-*ido*-, D-*gluco*-, or D-*galacto*-aldol stereoselectively, depending on the base used. Efficient transformation of the aldols has presented new syntheses of valiolamine (**5**) in 10 steps with 17.2% overall yield, validoxylamine G (**7**) in 12 steps with 15.1% overall yield, and a formal synthesis of voglibose (**6**). Since carbohydrates are abundant in nature, transformation of carbohydrates into carbocycles is a very important conversion because it provides valuable starting materials for making pharmaceuticals without shortage of supply. These cabasugars from carbohydrates should have broad application in chemical biology and could be exploited for a wide range of functionalized cyclohexenoid or cyclohexanoid targets and intermediates of pharmaceutical importance.

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Supporting Information Available: Experimental procedures and product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Preparation of new compounds is described in Supporting Information.

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