ORGANIC LETTERS

2000
Vol. 2, No. 4
457−460

Facile Ring Transformation from Gluconolactone to Cyclitol Derivative via Spiro Sugar Ortho Ester

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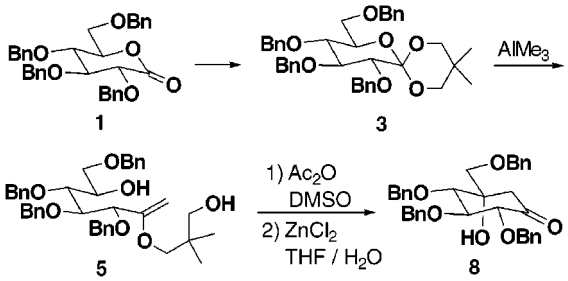
Received December 2, 1999

ABSTRACT



A short step preparation of cyclitol derivative 8 which is a versatile synthon for the synthesis of valiolamine and its related compounds is described. Key steps in this preparation are a novel enol ether formation from spiro sugar ortho esters with $AlMe_3$ and an intramolecular Aldol condensation of alkyl enol ethers catalyzed by $ZnCl_2$ in THF−H_2O. With these reactions, gluconolactone derivative 1 was efficiently converted into 8 in short steps.

Carbasugars and carbaaminosugars have attracted much attention due to their activities as glycosidase inhibitors, whose potential use as therapeutic agents against HIV infection and diabetes was recently recognized.[1] Various methods for the synthesis of these molecules have been developed, and the use of carbohydrates as synthetic precursors for cyclitol derivatives has been widespread.[2,3] In this paper, we report a novel and facile procedure for the effective conversion of gluconolactone to the cyclitol derivative **8**,[4] which is a versatile synthon for the synthesis of valiolamine,[5−7] and its derivatives including voglibose.[8] Compound **8** was

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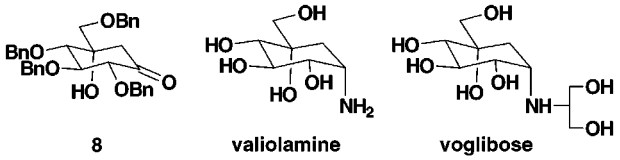
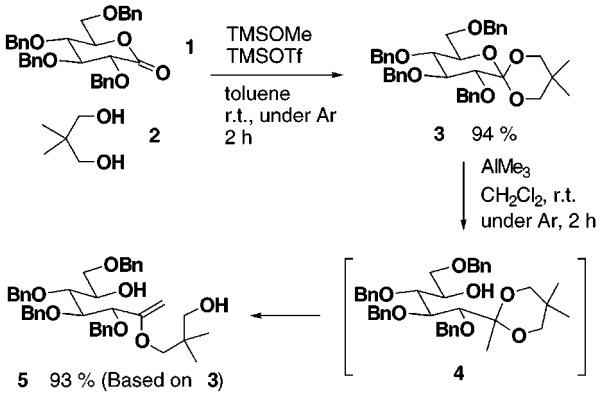
10.1021/ol9913035 CCC: $19.00
Published on Web 01/21/2000

recently synthesized by Fukase and Horii on the basis of the intramolecular Aldol condensation of the α,α-bis-(methylthio)- or α,α-dichlorocarbonyl compound; however, a desulfurization or dechlorination step was necessary to accomplish the preparation of this molecule using their method. In the procedure presented here, the alkyl enol ether compound that was prepared directly from a spiro sugar ortho ester by a novel methyl anion insertion and a subsequent ring opening reaction was used as the key intermediate, which shortened the steps for the preparation of **8** and improved the yield.



Recently, we have thoroughly explored the reactivity of sugar ortho esters for the purpose of developing the reductive glycosylation methods by which the glycosyl linkages are formed as the result of hydride anion attack to the spiro carbon atoms of the ortho ester molecules.[9] As an extension of this study, we investigated the reactivity of the methyl anion to sugar ortho esters and revealed that gluconolactone ortho ester was smoothly converted into an enol ether compound by treatment with $AlMe_3$. As shown in Scheme 1, ortho ester **3** which was prepared from lactone **1**[10] and

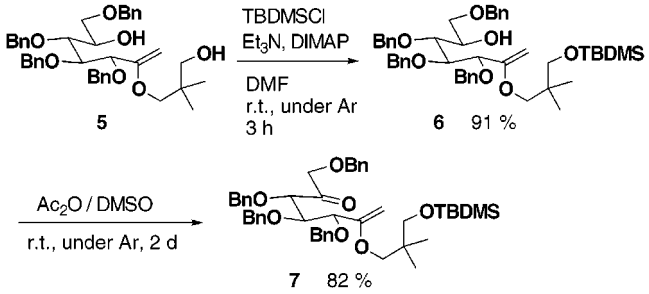
Scheme 1



2,2-dimethylpropanediol **2** in 94% yield according to the method previously reported[11] was treated with 5 equiv of $AlMe_3$ (1.0 M *n*-hexane solution) in CH_2Cl_2 for 2 h at room temperature to afford enol ether **5** in 93% yield. In the case with a smaller amount of aluminum reagent, ketal **4** was also detected as a product. TLC analysis revealed that **5** was formed via **4** under these conditions. Actually, isolated **4** was smoothly converted into **5**, by treatment with $AlMe_3$. These results indicated that the first step of this reaction was the cleavage of a pyran ring of the sugar moiety caused by the insertion of a methyl anion from $AlMe_3$ and the second step was cleavage of a dioxane ring accompanied by proton elimination.[12] The first step ring opening which was caused by the two-faced character of $AlMe_3$ was presumed to be assisted by the π-electrons of two oxygen atoms of a dioxane ring.[13]

As the resulting enol compound seemed to be a suitable precursor for the preparation of cyclitols based on the intramolecular Aldol condensation, we planned to develop a new method for the synthesis of these molecules and prepared a 5-keto species from **5** according to the conditions shown in Scheme 2. Treatment of **5** with TBDMSCl (2

Scheme 2



equiv), Et_3N (5 equiv), and DIMAP (0.2 equiv) in DMF provided the silyl-protected compound **6** in 91% yield,[14] which was converted into the keto derivative **7** by exposure to excess Ac_2O/DMSO. The yield of **7** was increased by changing the ratio between Ac_2O and DMSO to 1:4 from the usual 1:1; however, the keto product was partially decomposed during column chromatography to reduce the yield to 82%.

While the aldol condensation with silyl enol ethers[15] has been frequently used in products syntheses, there have been few reports on the related reaction with alkyl enol ethers recently.[16] Thus, the conditions for the cyclization of **7** were next investigated. As shown in Table 1, hydrolysis product **9** was the main product instead of the desired compound **8**

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(11) Yoshimura and co-workers previously reported the synthesis of interglycosidic spiro ortho esters (ref 11a) from sugar lactones and silylated diols using TMSOTf as the catalyst in a modification of Noyori's method (ref 11b). We also modified the process for ortho ester preparation (ref 11c) considering the acetal synthesis by Kurihara and Miyata (ref 11d). (a) Yoshimura, J.; Tamaru, M. *Carbohydr. Res.* **1979**, *72*, C9. (b) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357. (c) References 9a and 9c. (d) Kurihara, M.; Miyata, N. *Chem. Lett.* **1995**, 263.

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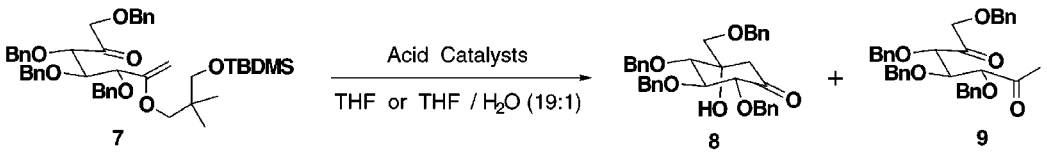
Table 1. Intramolecular Aldol Condensation of **7** with Acid Catalysts



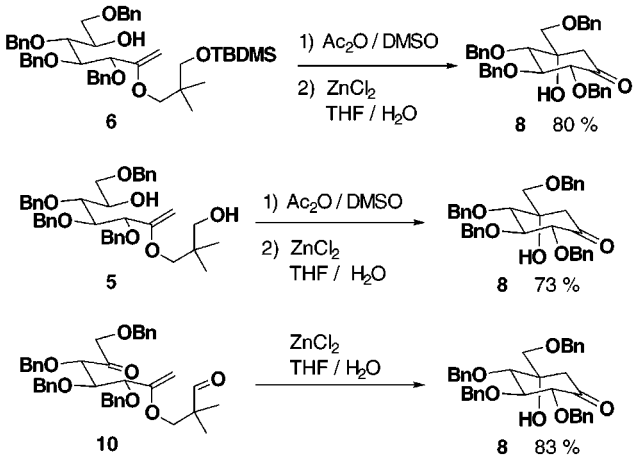
						% yield[c]		
entry	reagent	reagent/**7**	additive	temp	time	**8**	**9**	**7** (recovery)
1[a]	PPTS	1.0		rt	18 h	28	51	nd[d]
2[a]	BF_3·Et_2O	1.0		rt	15 mim	69	1	nd
3[a]	$ZnCl_2$	1.0		rt	18 h	68	nd	nd
4[b]	$ZnCl_2$	1.0	H_2O	rt	18 h	28	nd	67
5[b]	$ZnCl_2$	2.0	H_2O	rt	18 h	43	nd	50
6[b]	$ZnCl_2$	2.0	H_2O	reflux	4 h	90	nd	nd
7[b]	HCl	2.0	H_2O	rt	30 min	4	62	nd
8[b]	$La(OTf)_3$	1.0	H_2O	rt	18 h	9	nd	84
9[b]	$YbCl_2$·$6H_2O$	1.0	H_2O	rt	24 h	trace[e]	nd	91

[a] Reactions were carried out in THF. [b] Reactions were carried out in THF/H_2O (19:1). [c] Isolated yields based on **7**. [d] Not detected. [e] <0.5%.

when PPTS was used as an acid catalyst (entry 1). With $ZnCl_2$ or BF_3·Et_2O in nonaqueous solvent (entries 2 and 3), the formation of **9** was suppressed; however, the yield of **8** was less than 70% because of the undesired side reaction and product decomposition. Remarkably, it was revealed that the addition of water improved the product selectivity in the $ZnCl_2$-catalyzed cyclization of **7** (entries 4 and 5). Although the rate of the reaction was reduced by the additon of water (entry 4 vs 3), the reaction with 2 equiv of the catalyst under reflux conditions proceeded efficiently to afford **8** in 90% yield (entry 6). Since the product distribution in the reaction with HCl was far different from that in the case with $ZnCl_2$ (entry 7 vs 5), it seemed rational to assume that the zinc complex catalyzed the reaction instead of a proton in aqueous solvent. Water might change the reactivity of $ZnCl_2$ by coordination to a metal center or might assist the reaction by providing an excess amount of hydroxy units. Recently, aldol condensation of silyl enol ethers with various metal catalysts in aqueous THF was reported.[17] As shown in entries 8 and 9, $La(OTf)_3$ or $YbCl_3$·$6H_2O$, which were efficient catalysts for the reaction with silyl enol ethers, were not as effective as $ZnCl_2$ for this cyclization (entries 8 and 9 vs 4), which might be explained by considering the steric hindrance of large lanthanide complexes.

As described above, the 5-keto enol ether **7** was not stable in a silica gel column; however, it was revealed that column purification of **7** was not necessary for efficient cyclization under the above conditions. After the usual workup (washing with H_2O), crude **7** was treated with $ZnCl_2$ in THF/H_2O and converted into **8** in 80% yield based on **6** (Scheme 3). More practically, oxidation of **5** followed by cyclization of the crude oxidation products according to the same procedure used for the silyl-protected enol ether **6** afforded **8** in 73% yield based on **5** (Scheme 3). The main product of the oxidation of **5** was the dioxo species **10** which was generated by the oxidation of both of 1°- and 2°-alcohols. The 5-keto species with a methylthiomethyl functionality on the 1°-alcohol whose type of byproduct was often detected in Ac_2O/DMSO oxidation was also obtained. Fortunately, the enol ether moiety of **10** selectively reacted with ketone in sugar under the above conditions to afford **8** in 83% yield (Scheme 3); thus the desired product was obtained in good yield directly from **5**. The process presented here with few steps and a 64% total yield based on **1** provides a facile and efficient method for the synthesis of **8** and may be a new practical entry for the preparation of cyclitols. Extension of this study is now under investigation in this laboratory.

Scheme 3



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Acknowledgment. We are grateful to Misses J. Shimode, J. Nonobe, and M. Kitsukawa for spectroscopic measurements. Partial financial support for this research from the Ministry of Education, Science, Sports and Culture of Japan is gratefully acknowledged.

OL9913035