

Nucleophilic Addition Reaction of 2-Trimethylsilyloxyfuran to *N*-Gulosyl-*C*-alkoxymethylnitrones: Synthetic Approach to Polyoxin C

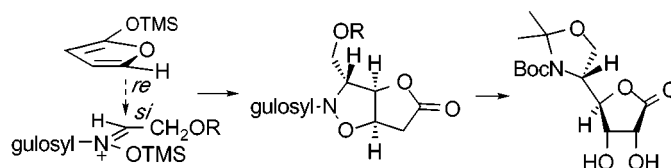
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ABSTRACT



The stereoselectivity of nucleophilic addition of 2-trimethylsilyloxyfuran to *N*-gulosyl-*C*-alkoxymethylnitrones was investigated. It was found that the selectivity was highly dependent on the bulkiness of the *C*-substituent of the nitron. The major adducts were elaborated into the key intermediate of polyoxin C.

Polyoxin Cs, the hybrid compounds of nucleosides and α -amino acids, are important as the *C*-terminal amino acid components of nikkomycins, which exhibit antifungal activity.¹ Therefore, the stereoselective synthesis of the unique amino acid has been intensively investigated.² In connection with our synthetic program of nikkomycin Bz (**1**), a novel route to polyoxin C (**3**) was sought (Scheme 1). In our previous study³ of *N*-terminal amino acid component **2** employing intramolecular cycloaddition of *N*-(2,3:5,6-*O*-dicyclohexylidene-*L*-gulosyl)-*C*-(*p*-methoxycinnamyloxycarbonyl)nitron (**A**), the protected *L*-gulosyl group played a key role of the stereoselection as the chiral auxiliary. We envisioned stereoselective construction of the ribofuranosyl

amino acid framework (indicated in the box in **3**),⁴ the essential structure for polyoxin C, by the use of nucleophilic

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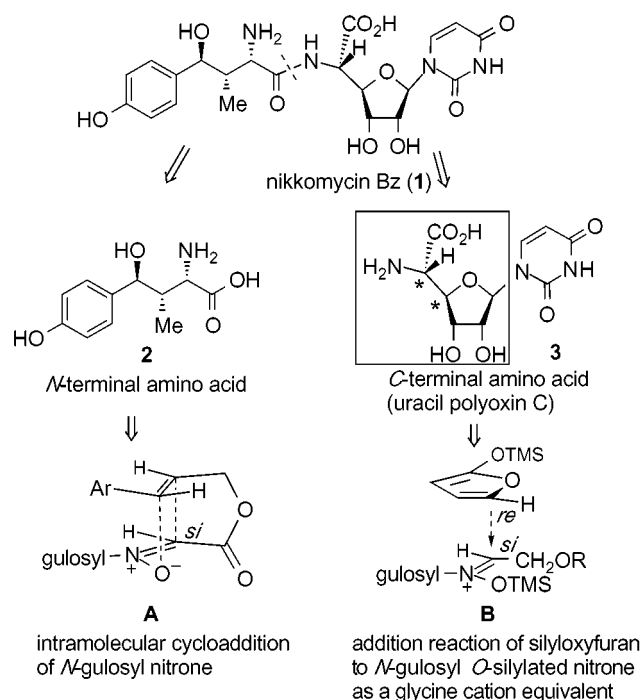
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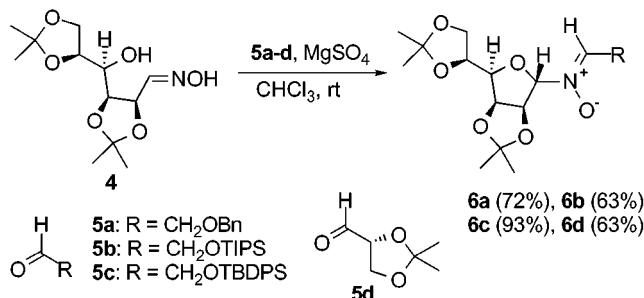
Scheme 1



addition of 2-silyloxyfuran to *O*-silylated *N*-(L-gulosyl)-nitron as the glycine cation equivalent **B**.^{4–8} We present here the addition reaction of the silyloxyfuran to *N*-(2,3:5,6-*O*-diisopropylidene-L-gulosyl)-*C*-(alkoxymethyl)nitron with high diastereoselectivity and diastereofacial selectivity and application of the reaction to synthesis of the key intermediate to polyoxin C.

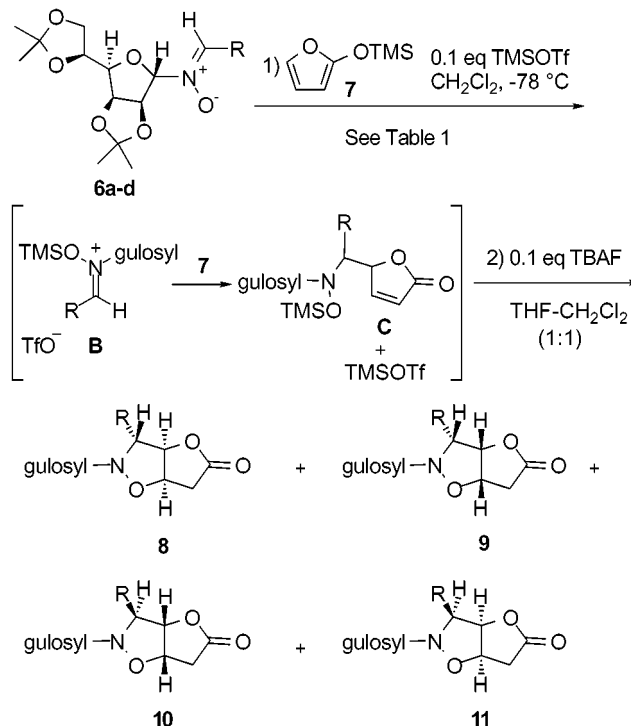
Four types of (*Z*)-*N*-(2,3:5,6-*O*-diisopropylidene-L-gulosyl)-*C*-(alkoxymethyl)nitrones (**6a–d**) were prepared by condensation of 2,3:5,6-*O*-diisopropylidene-L-glucose oxime (**4**)⁹ with α -alkoxyaldehydes (**5a–d**) in chloroform in the presence of magnesium sulfate (Scheme 2).

Scheme 2



On treatment of nitrones **6** with 2-trimethylsilyloxyfuran (**7**) in the presence of catalytic amounts of TMSOTf in CH₂-Cl₂ at –78 °C, a smooth addition reaction took place and was completed within 15 min to give initially unstable products **C**, which afforded stable bicyclic products **8** as

Scheme 3



major products accompanied by the other diastereomers **9–11** after workup with TBAF (Scheme 3). The stereoselectivities of the addition reactions were highly dependent on the bulkiness of *C*-substituents of nitrones **6** (Table 1).

Table 1. Addition Reaction of Nitrones **6a–d** with Silyloxyfuran **7**

Entry	Nitrone 6 (R)	Yield (%)	Ratio 8 :(9 + 10 + 11)
1	6a (CH ₂ OBn)	84	76:(13+8+3)
2	6b (CH ₂ OTIPS)	80	74:(21+5)
3	6c (CH ₂ OTBDPS)	80	86:(8+6)
4	6d (CH ₂ OR)	72	>97:3>

Thus, the reaction of *C*-benzyloxymethylnitrone **6a** produced a mixture of four diastereomers in a ratio of 76:13:8:3 and in 84% combined yield (entry 1). More hindered *C*-triisopropylsilyloxymethylnitrone **6b** gave a mixture of three

(5) For an excellent review for addition of organometallic reagents to C=N bonds, see: Bloch, R. *Chem. Rev.* **1998**, 98, 1407–1438.

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(7) For reviews for nucleophilic additions of 2-silyloxyfurans, see: (a) Casiraghi, G.; Rassu, G. *Synthesis* **1995**, 607–626. (b) Rassu, G.; Zanardi, F.; Battistini, L.; Casiraghi, G. *Synlett* **1999**, 1333–1350. (c) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, 57, 3221–3242.

diastereomers, and the use of *tert*-butyldiphenylsilyloxy-methylnitrone **6c** afforded improved selectivity (entries 2 and 3). Nitrone **6d** having a branched substituent derived from D-glyceraldehyde **5d** afforded the single stereoisomer **8d** (entry 4).¹⁰

The substituent effect in stereoselectivity may be explained by taking into account the bulkiness of the initially generated silyloxyiminium intermediate **B** (Figure 1). In the case of

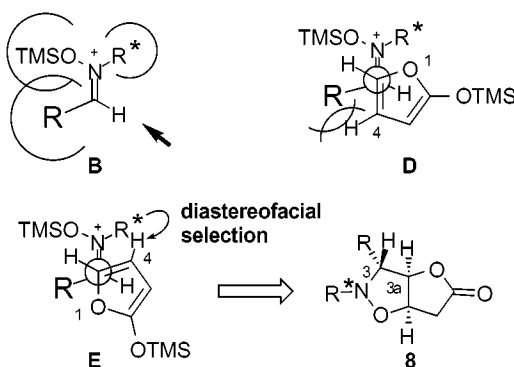


Figure 1.

nitrone **6c** or **6d** having a bulky C-substituent, silyloxyfuran **7** seems to approach from the vacant region around the hydrogen atom indicated by a bold arrow, since the other space may be filled with the substituents. Therefore, transition state models **D** and **E** may be considered (to simplify, only upper face approaches of silyloxyfuran **7** to silyloxyiminium cation **B** are represented in Figure 1). Transition states **D** and **E** give opposite relative 3,3a-stereochemistries to each other. Since the 4-position of the furan is apparently bulkier than the 1-position, the use of a nitrone having a sterically more demanding C-substituent makes model **E** more favored than model **D**. Transition state **E** may exhibit high diastereofacial selectivity because of the closeness between the 4-position and the chiral auxiliary, whereas both antipodal transition states would be possible in the case of **D**. Accordingly, the use of bulky nitrones having a tendency to form **E** shows good diastereoselectivity and diastereofacial selectivity to afford **8**.¹¹

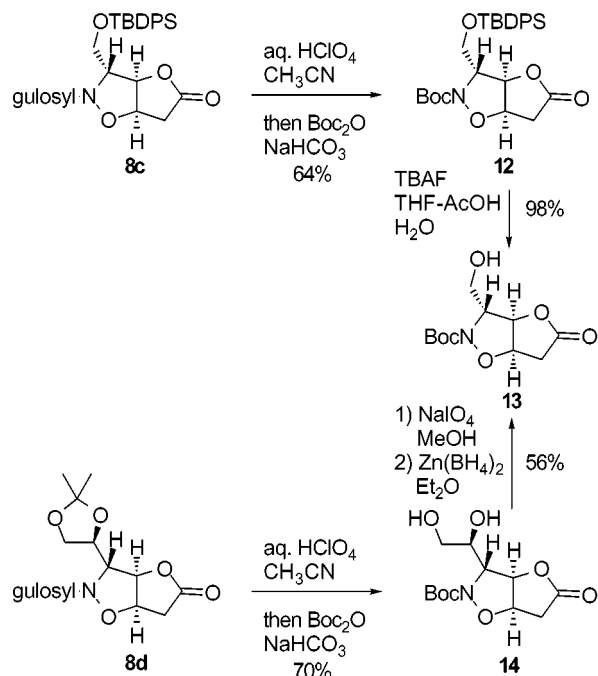
(8) For nucleophilic additions to *N*-glycosyl nitrones, see: (a) Huber, R.; Knieringer, A.; Obrecht, J.-P.; Vasella, A. *Helv. Chim. Acta* **1985**, *68*, 1730–1747. (b) Mancini, F.; Piazza, M. G.; Trombini, C. *J. Org. Chem.* **1991**, *56*, 4246–4252. (c) Basha, A.; Henry, R.; McLaughlin, M. A.; Ratajczyk, J. D.; Wittenberger, S. J. *J. Org. Chem.* **1994**, *59*, 6103–6106. (d) Rohloff, J. C.; Alfredson, T. V.; Schwartz, M. A. *Tetrahedron Lett.* **1994**, *35*, 1011–1014. (e) Lantos, I.; Flisak, J.; Liu, L.; Matsuoka, R.; Mendelson, W.; Stevenson, D.; Tubman, K.; Tucker, L.; Zhang, W.-Y.; Adams, J.; Sorenson, M.; Garigipati, R.; Erhardt, K.; Ross, S. *J. Org. Chem.* **1997**, *62*, 5385–5391.

(9) The oxime was prepared by a similar method for dicyclohexylidene congener of **4**, see: (a) Iida, H.; Kasahara, K.; Kibayashi, C. *J. Am. Chem. Soc.* **1986**, *108*, 4647–4648. (b) Kasahara, K.; Iida, H.; Kibayashi, C. *J. Org. Chem.* **1989**, *54*, 2225–2233.

(10) It is known that addition reaction of *N*-benzyl congener of **6d** with **7** in the presence of TMSOTf gives four stereoisomers of adduct with very low stereoselectivity. The stereoselectivity of the present reaction of **6d**, therefore, may be mainly due to the effect of the sugar auxiliary. See: Degiorgis, F.; Lombardo, M.; Trombini, C. *Tetrahedron* **1997**, *53*, 11721–11730.

The major bicyclic products **8c** and **8d** were readily isolated and employed for synthetic studies on C-terminal amino acids of nikkomycin Bz. Hydrolytic removal of the sugar auxiliary of **8c** gave **12** after protection of the nitrogen atom by treatment with Boc₂O (Scheme 4). *N*-Protected

Scheme 4

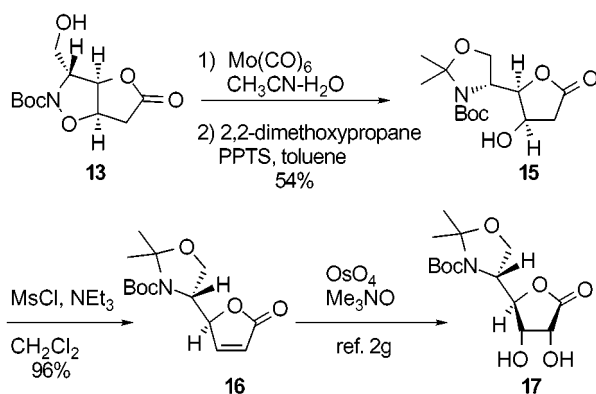


compound **12** was led to alcohol **13** by desilylation under the mild condition of TBAF–AcOH–THF. Adduct **8d** was treated by HClO₄ followed by Boc₂O in a similar way for **8c** to afford diol **14**. Diol **14** was transformed into **13** by oxidative cleavage with NaIO₄ and reduction with Zn(BH₄)₂. Concordant specific rotations of **13** herein obtained, [α]_D²¹ –23.1 (*c* 0.96 CHCl₃) from **8c**; [α]_D²¹ –22.1 (*c* 0.81 CHCl₃) from **8d**, confirmed that **8c** and **8d** have the same stereochemistry on the bicyclic systems.

Reductive cleavage of the N–O bond of **13** by heating with molybdenum hexacarbonyl in acetonitrile–water and subsequent treatment with 2,2-dimethoxypropane in the presence of a catalytic amount of PPTS in toluene produced acetonide **15** (Scheme 5). Treatment of acetonide **15** with MsCl and triethylamine caused dehydration to give butenolide **16**. Finally, dihydroxylation of **12** by the reported method^{2g} gave known ribonolactone–amino acid derivative **17**,^{2g} [α]_D²¹ +31.0 (*c* 0.85, CHCl₃), lit.^{2g} [α]_D²¹ +31.8 (*c* 0.87, CHCl₃), a key intermediate of polyoxin C.

(11) Trombini et al. reported the reaction of **7** with an *N*-benzyl nitrone derived from *O*-benzyl lactate. They proposed a π–π interaction of **7** with the *N*-benzyl group, see: Castellari, C.; Lombardo, M.; Pietropaolo, G.; Trombini, C. *Tetrahedron: Asymmetry* **1996**, *7*, 1059–1068. Martin et al. expanded the Diels–Alder type transition state (DATS) model for the reaction of silyloxyiminium ion with **7**.^{7c} In the present reaction, DATS giving the major isomer **8** would demand that C(4) carbon of **7** should occupy a very close position to the R group of iminium ion **B**. However, the reaction of nitrone **6** bearing a bulkier R group gave a higher ratio of **8**. Consequently, it seems to be reasonable to assume model **E** for the formation of **8** instead of DAST.

Scheme 5



In conclusion, we have explored the stereoselective addition reaction of 2-silyloxyfuran to *N*-gulosylnitrone. This is the first example showing that stereoselectivity

of the silyloxyfuran–nitrone addition reaction can be controlled by the *N*-chiral auxiliary of the nitrone. It was also found that a nitrone having bulkier *C*-substituent gives a better stereoselectivity. The products **8c** and **8d** of the present reaction could be successfully applied to the synthesis of the *C*-terminal amino acid component of nikkomycin Bz.

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Supporting Information Available: Spectroscopic data for all new compounds, as well as detailed experimental procedures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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