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# Intramolecular Cycloaddition of α-Allyloxycarbonylnitrone Bearing a Chiral Sugar Auxiliary: A Short-Step Synthesis of the *N*-Terminal Amino Acid Component of Nikkomycin Bz#

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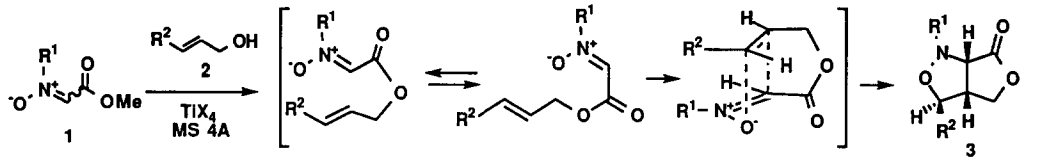
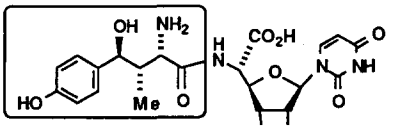
***Abstract:*** Heating 2,3:5,6-*O*-dicyclohexylidene-L-gulose oxime with methyl glyoxylate hemiacetal followed by treatment of the resulting mixture with allyl alcohols in the presence of catalytic amounts of titanium tetrachloride and molecular sieves 4A caused tandem nitrone formation, transesterification, *E,Z*-isomerization and diastereofacial selective intramolecular cycloaddition to provide stereocontrolled polycyclic compounds in one step. This method could be applied efficiently to synthesis of the *N*-terminal amino acid component of nikkomycin Bz. Copyright © 1996 Elsevier Science Ltd

Intramolecular cycloaddition of nitrones is recognized as a powerful method for construction of various nitrogen-containing carbon frameworks, since it enables regio- and stereoselective polycyclization in one step.[1] In this category, we recently reported that α-methoxycarbonylnitrones (**1**) cause tandem transesterification with allyl alcohols (**2**), *E,Z*-isomerization, and intramolecular cycloadditions in the presence of a titanium catalyst and molecular sieves to give stereocontrolled polycyclic products (**3**) under mild conditions in one step.[2] It was also reported that use of chiral (*Z*)-secondary allyl alcohol or combined use of chiral (*E*)-secondary allyl alcohol and chiral nitrone efficiently causes asymmetric induction to control three contiguous stereogenic centers newly formed in the cyclic system.[3]




In connection with synthetic study of nikkomycin Bz as an application of the tandem reaction, an efficient chiral auxiliary as $R^1$ of the nitrone (**1**), which is readily removable was required. In this communication, we report asymmetric induction of the tandem process of the nitrone bearing a sugar moiety[4] as the auxiliary, and its application to a short-step synthesis of the *N*-terminal amino acid component of nikkomycin Bz.[5,6]




Nikkomycin Bz

# Dedicated to the memory of Professor Wolfgang Oppolzer.

The starting sugar oxime, 2,3:5,6-*O*-dicyclohexylidene-L-gulose oxime, (**4**) was readily prepared from commercially available L-gulonic-γ-lactone by reported method.[4f] The oxime (**4**) was heated with methyl glyoxylate hemiacetal (**5**) in refluxing toluene. Then the solution was treated with a mixture of allyl alcohol (**7**), a catalytic amount of titanium tetrachloride and molecular sieves 4A to give major cycloadducts (**9a**) and minor cycloadducts (**9b**). The sequential processes involve formation of unisolable nitrone (**6**), transesterification to α-allyloxycarbonylnitrone (**8**), *E,Z*-isomerization of **8** and intramolecular cycloaddition *via* transition state (**A**) into **9a** and/or transition state (**B**) into **9b**, as shown in **Scheme 1**.

**Scheme 1**

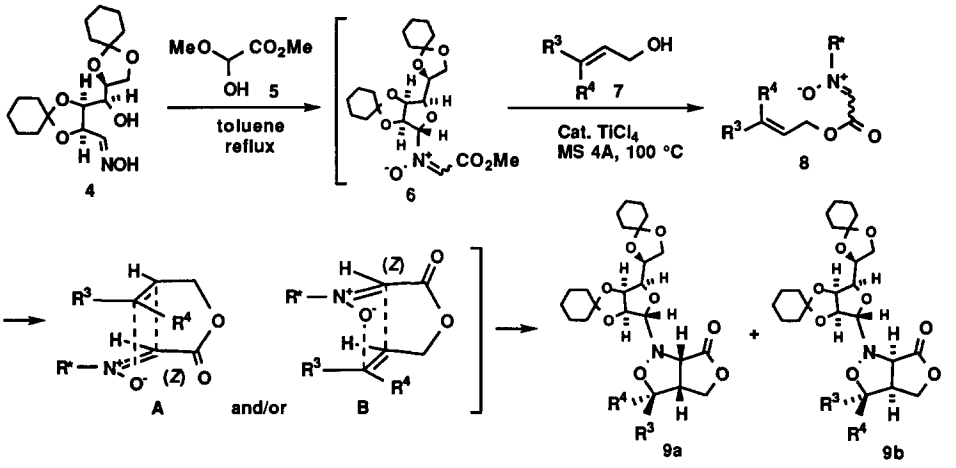
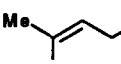
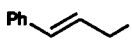



**Table 1.** Tandem nitrone formation from the sugar oxime (**4**) and methyl glyoxylate hemiacetal (**5**), transesterification with allyl alcohols (**7**), and intramolecular cycloaddition.

| Entry | Allyl Alcohol | Conditions | Yield (%) | Ratio[a] **9a : 9b** |
|---|---|---|---|---|
| 1 |  **7a** (5 eq.) | 0.1 eq. $TiCl_4$, toluene-$ClCH_2CH_2Cl$ (2:1), reflux, 8 hr | 74 | 2 : 1 |
| 2 |  **7b** (1.5 eq.) | 0.1 eq. $TiCl_4$, toluene-$ClCH_2CH_2Cl$ (1:1), 100 °C, 2.5 hr | 69 | 4 : 1[b] |
| 3 |  **7c** (1.5 eq.) | 0.1 eq. $TiCl_4$, toluene-$ClCH_2CH_2Cl$ (1:2), 100 °C, 3 hr | 85 | 3 : 2 |
| 4 |  **7d** (1.5 eq.) | 0.2 eq. $TiCl_4$, toluene-$ClCH_2CH_2Cl$ (1:2), 100 °C, 8 hr | 77 | 1 : 0 |

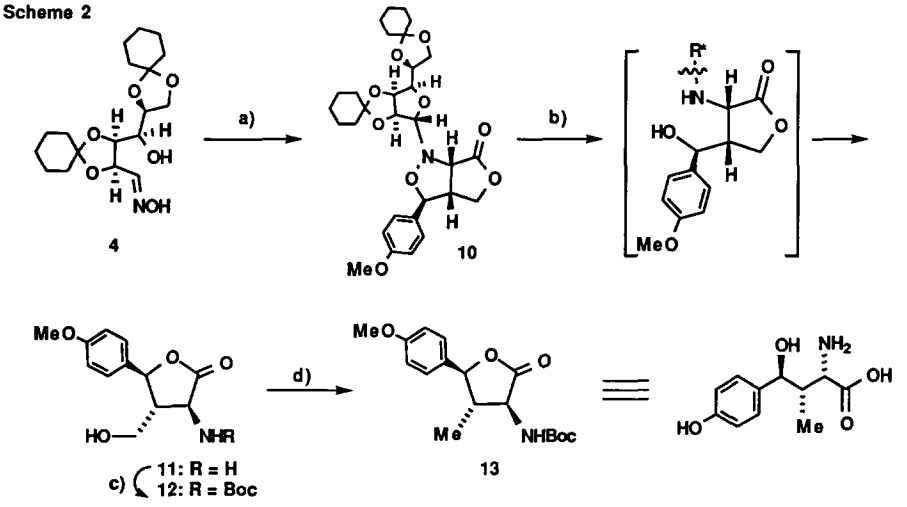
a) Unless otherwise noted, the ratios were obtained from the 270 MHz $^1$H-NMR.

b) The ratio is based on the isolated yields of the diastereomers.

The results employing several allyl alcohols (**7a-d**) are summarized in **Table 1**.[7] The diastereofacial selectivities of the intramolecular cycloaddition are highly dependent on the structure of **7a-d**. While the reactions employing **7a** and **7c** (entries 1 and 3) gave poor selectivities, the reactions using **7b** and **7d** gave good to excellent selectivities (entries 2 and 4). These differences in selectivity would be rationalized by considering transition states (**A** and **B**) in the cycloaddition step. Since the intramolecular cycloaddition proceeds from (*Z*)-nitrone,[2,3] the *trans*-substituent ($R^3$) in both **A** and **B** is oriented in the *endo* position, which would be very close to the auxiliary (R*) and strongly influenced by chiral circumstances of R*. Accordingly, the use of **7b** and **7d** having the $R^3$ group gave better selectivities (entries 2 and 4).

This tandem methodology was successfully applied to the straightforward synthesis of the *N*-terminal amino acid moiety of nikkomycin Bz. Thus, treatment of the oxime (**4**) with **5** followed by heating with (*E*)-*p*-methoxycinnamyl alcohol, a catalytic amount of titanium tetrachloride, and MS 4A gave the corresponding intramolecular cycloadduct (**10**), mp 94-96 ℃, $[\alpha]^{21}_D$ +9.1 (*c* 0.99, $CHCl_3$), as the sole product in 75% yield. The adduct (**10**) already has all the correct stereogenic centers of the target molecule. Reductive cleavage of the *N-O* bond of **10** by heating with molybdenum hexacarbonyl in acetonitrile-water (10 : 1)[8] and subsequent treatment with diluted hydrochloric acid caused hydrolytic removal of the sugar auxiliary and recyclization to generate **11**. Without purification of **11**, the primary amino functionality was protected by the *tert*-butyloxycarbonyl group to furnish **12**, $[\alpha]^{21}_D$ +55.6 (*c* 1.69, $CHCl_3$), in 53% yield from **10**. Finally, mesylation of the primary hydroxyl group of **12** followed by treatment with sodium iodide and tributyltin hydride[9] yielded the desired lactone (**13**), $[\alpha]^{21}_D$ +20.6 (*c* 1.17, $CHCl_3$), *lit.*[6d] $[\alpha]^{21}_D$ +20.1 (*c* 0.82, $CHCl_3$), which is known as the nikkomycin Bz *N*-terminal amino acid component.[5d,6d,e]

Scheme 2




a) methyl gyoxylate hemiacetal (**5**), toluene, reflux, then (*E*)-*p*-methoxycinnamyl alcohol, Cat. $TiCl_4$, MS 4A, 100 °C, 75% from **4** b) $Mo(CO)_6$, $CH_3CN$-$H_2O$ (10 : 1); 1% HCl-$CH_3CN$ c) $Boc_2O$, $CH_3CN$, 53% from **10** d) MsCl, $NEt_3$, $CH_2Cl_2$; NaI, *n*-$Bu_3SnH$, DME, 80 °C, 65% from **12**

As mentioned above, we have successfully explored a one-pot method which involves *in situ* formation of nitrone having a sugar moiety, transesterification, *E,Z*-isomerization, and diastereofacial selective intramolecular cycloaddion. This methodology could be applied to a short-step synthesis of the *N*-terminal

amino acid moiety of nikkomycin Bz. Since both enantiomers of the starting oxime (**4**) are available,[4f] this tandem proccess may be useful for other asymmetric syntheses.

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