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Efficient and Stereoselective Synthesis of the Disaccharide Fragment of Incednine

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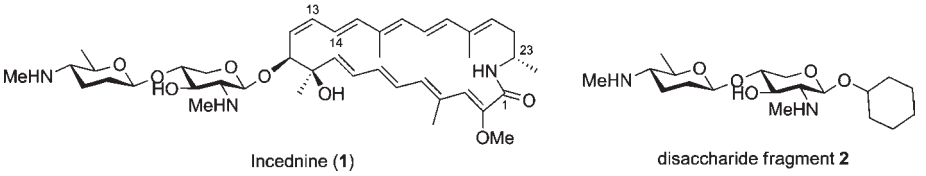
ABSTRACT



Efficient and stereoselective synthesis of a disaccharide fragment, 2-deoxy-4-*O*-(*N*-monodemethyl-D-forosaminyl)-2-methylamino-β-D-xylopyranoside, of a novel antibiotic, incednine (1), is described. The key β-stereoselective formation of a 2,3,4,6-tetradeoxy-4-methylamino glycoside bond was achieved by remote participation-assisted glycosylation.

Incednine (**1**), a novel macrolactam glycoside antibiotic that was isolated from *Streptomyces* sp. by Imoto and coworkers,[1] exhibits significant inhibitory activity against the antiapoptotic oncoproteins Bcl-2 and Bcl-xL, with a mode of action different from those of other inhibitors. It is known that these proteins are overexpressed in many cancer cells, resulting in the expansion of transformed populations and advancement of the multi-drug-resistant stage.[2−4] Therefore, **1** is expected to be of importance in the development of novel antitumor drugs. Furthermore, **1** is likely to be a useful tool for further study of the functions of Bcl-2 and Bcl-xL. Structurally, **1** contains several unique features: an α-methoxy-α,β-unsaturated amide moiety, two independent conjugated polyene systems embedded in the 24-membered macrolactam ring, and a disaccharide fragment comprising two unusual deoxyamino sugars, *N*-monodemethyl-D-forosamine and 2-deoxy-2-methylamino-D-xylose, attached by β-glycoside bonds.

Because of its important biological activity and novel molecular architecture, **1** has been a prime target for chemical synthesis. We recently reported the total synthesis of incednam, the aglycon of **1**, employing a Stille coupling reaction and macrolactamization as key steps,[5] with efficient and stereoselective construction of the disaccharide domain as the remaining task in the synthesis of **1**.

The highly deoxygenated 2,3,4,6-tetradeoxy-4-methylamino-β-glycoside residue *N*-monodemethyl-β-D-forosaminide is known as one of the most acid-labile glycoside linkages.[6] In addition, stereoselective and direct construction of the 2,3,6-trideoxy-β-glycoside linkage by glycosylation is a difficult and challenging task for synthetic chemists due to the missing control element at the C-2 position.[7] Herein we report the stereoselective synthesis of the disaccharide fragment (**2**) of incednine (**1**) employing a highly β-selective and direct glycosylation assisted by remote and neighboring group participation as key steps.

The retrosynthetic analysis of **2** is depicted in Figure 1. We envisaged that the desired disaccharide **2** could be derived by β-selective glycosylation of the disaccharide

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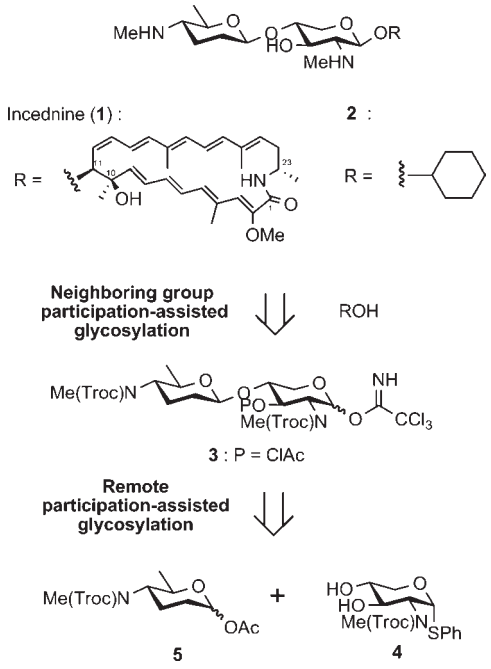


Figure 1. Retrosynthetic analysis of the disaccharide fragment **2**.

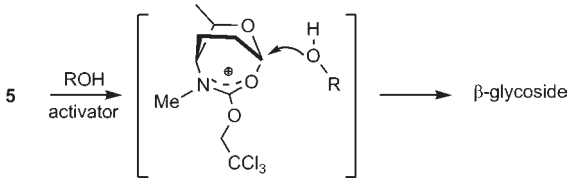
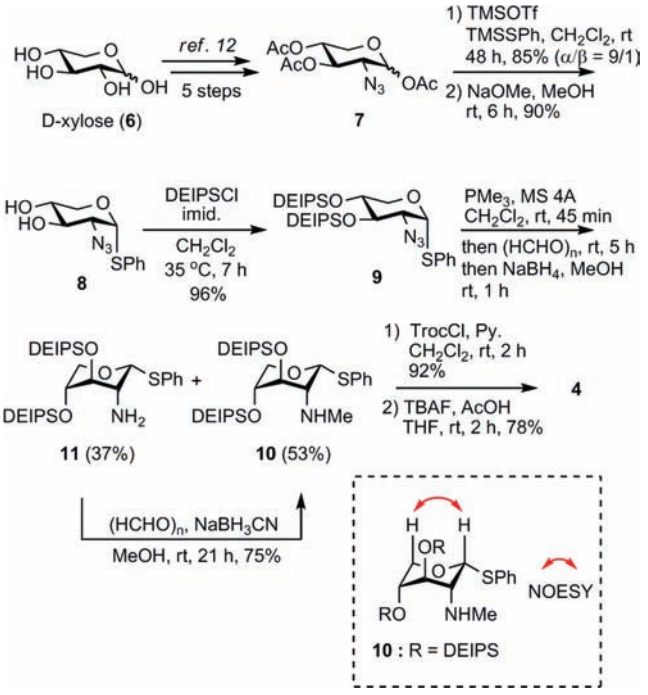


Figure 2. Presumed mechanism for remote participation-assisted β-selective glycosylation.

imidate **3** using a mild Lewis acid activator, such as $Yb(OTf)_3$,[8] assisted by participation of the neighboring 2-*N*-carbamoyl group,[8] without anomerization or cleavage of the preinstalled 2,3,4,6-tetradeoxy-4-methylamino-β-glycoside bond. For the *N*-carbamoyl group at the C-2 position, we chose a *N*-trichloroethoxycarbamoyl (Troc) group because it is widely used in neighboring group-assisted glycosylations[9] and easy to remove under mild conditions. For the stereoselective formation of a *N*-monodemethyl-β-D-forosaminide bond in the glycosyl donor **3**, we focused on remote participation-assisted glycosylation using **5**, which possesses a Troc group at the C-4 position (Figure 2). In our previous study on the glycosylation of D-olivoses and D-olivosyl phosphates, which possess different protecting groups at the C-3 and C-4 positions, in the presence of montmorillonite K-10 as an activator, a 3-*O*-TBS-4-*O*-Ac or 3-*O*-Bn-4-*O*-Bz donor was found to show better β-selectivity than 3,4-di-*O*-Bn donors, probably due to the participation effect of the C-4 acyl protective groups.[10] In addition, other reports have noted that remote participation of the C-4 acyl group induced β-selectivity in mannosylations and glucosylations.[11] On the basis of these previous findings, we expected that the glycosyl donor **5**, with high conformational flexibility, would facilitate the remote participation of the *N*-Troc group at the C-4, and glycosylation with acceptor **4** would proceed effectively to give the corresponding disaccharide with high β-selectivity.

Scheme 1. Synthesis of Glycosyl Acceptor **4**



The synthesis of the 2-deoxy-2-methylamino-D-xylopyranoside derivative **4** is summarized in Scheme 1. Preparation of the known sugar **7** from D-xylose (**6**) was achieved based on the Hashimoto's procedure,[12] and **7** led to the corresponding thioglycoside as a mixture of anomeric isomers (α/β = 9/1) by treatment with TMSOTf and TMSSPh. Deprotection of the acetyl groups provided **8**, and then the separated α-anomer was protected as a diethylisopropylsilyl (DEIPS) ether.[13] The azide group of

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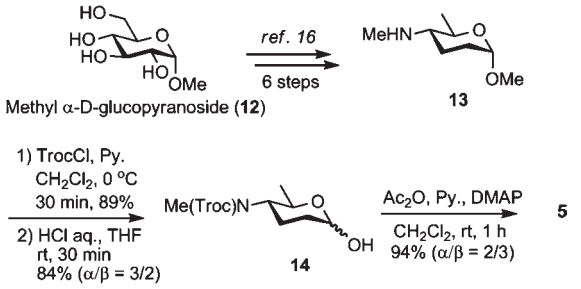
9 was converted to the corresponding *N*-monomethylamine **10** by a convenient one-pot procedure reported by Suzuki and co-workers.[14] At this stage, conformational change, in which the typical $^4C_1$ conformation flipped to the less common $^1C_4$ conformation, was confirmed by NOESY correlation between H-1 and H-5. This phenomenon was previously reported by Matsuda and Shuto when bulky and robust *tert*-butyldimethylsilyl protecting groups were installed at the C-3 and C-4 positions of xylopyranoside derivatives.[15] The undesired amino sugar **11**, which was produced along with **10**, could be converted to the *N*-monomethylamino sugar **10** via reductive amination in 75% yield. The *N*-methylamino group was protected as a trichloroethoxycarbamate, and subsequent deprotection of the DEIPS groups gave the glycosyl acceptor **4**. Meanwhile, glycosyl donor **5** was prepared from methyl α-D-glucopyranoside (**12**), as shown in Scheme 2. The known methylglycoside **13** was synthesized in six steps, referring to Baer's methodology.[16] The *N*-methylamino group of **13** was protected by a Troc group, and subsequent hydrolysis and acetylation gave the glycosyl donor **5**.

Scheme 2. Synthesis of Glycosyl Donor **5**



With both glycosyl acceptor **4** and donor **5** in hand, we examined the glycosylation reaction under various conditions to investigate how the *N*-Troc group at the C-4 position of **5** affected the stereoselectivity of the reaction. The results are summarized in Table 1. It was found that glycosylation of **4** (1.5 equiv) with **5** (1.0 equiv) in the presence of TMSOTf (0.3 equiv) and 5 Å molecular sieves (100 wt % with respect to **5**) in CH_2Cl_2 at −60 °C proceeded smoothly to provide the desired β-(1,4)-linked deoxyglycoside **15*β***, the α-(1,4)-linked deoxyglycoside **15α**, and the β-(1,3)-linked deoxyglycoside **16*β*** in yields of 31, 58, and 6%, respectively, with excellent regioselectivity and poor stereoselectivity (entry 1). The configuration of the anomeric positions of **15** and **16** was clearly confirmed by the corresponding amino products which were obtained after deprotection of the Troc groups. The high regioselectivity was, presumably, due to low steric

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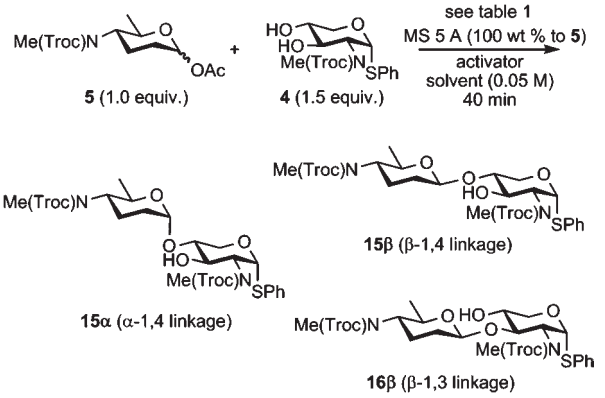
Table 1. Stereo- and Regioselective Glycosylation of **4** with **5**



				yield (%)		
entry	activator	solvent	temp (°C)	**15*β***	**15α**	**16*β***
1	TMSOTf (0.3 equiv)	CH_2Cl_2	−60	31	58	6
2	TMSOTf (0.3 equiv)	CH_2Cl_2	−40	69	9	20
3	TMSOTf (0.3 equiv)	CH_2Cl_2	−20	66	7	17
4	TMSOTf (0.3 equiv)	MeCN	−40	29	54	12
5	TMSOTf (0.3 equiv)	Et_2O	−40	10	70	
6	TMSOTf (0.3 equiv)	toluene	−40	67	13	9
7	$BF_3 \cdot OEt_2$ (1.5 equiv)	CH_2Cl_2	−40	42	35	9
8	$BF_3 \cdot OEt_2$, (1.5 equiv)	CH_2Cl_2	−20	68	13	17

hindrance at the C-4 position. However, the pyranose chair flip, which induces remote participation, did not take place effectively at −60 °C; therefore, the reaction was also examined at −40 and −20 °C. The β-selectivity of disaccharide **15** was dramatically improved, as expected, and the desired disaccharide **15*β*** was obtained in 69 and 66% yields, respectively (entries 2 and 3). Next, the solvent effect on the glycosylation reaction was investigated using MeCN, Et_2O, and toluene at −40 °C.

Interestingly, when a polar solvent, MeCN or Et_2O, was used, the stereoselectivity of **15** was found to change from β to α, and **15α** was obtained as the major product (entries 4 and 5); in contrast, when an apolar solvent, CH_2Cl_2 or toluene, was used, the desired **15*β*** was obtained as the major product (entries 2 and 6). These results suggested that polar solvents that can coordinate to an oxocarbenium intermediate prevented conformational change of the pyranose ring and remote participation of the *N*-Troc group at the C-4 position, leading to decreased β-selectivity.

In order to determine whether the major factor controlling β-selectivity was the remote participation effect of the *N*-Troc group at the C-4 or the formation of a glycosyl α-triflate intermediate,[17] we performed the glycosylation reaction using $BF_3 \cdot OEt_2$ (1.5 equiv) instead of TMSOTf as an activator in CH_2Cl_2 at −40 and −20 °C (entries 7 and 8). Although the glycosylation reaction at −40 °C afforded the desired disaccharide **15** in high yield with low β-selectivity, the β-selectivity was found to be improved by

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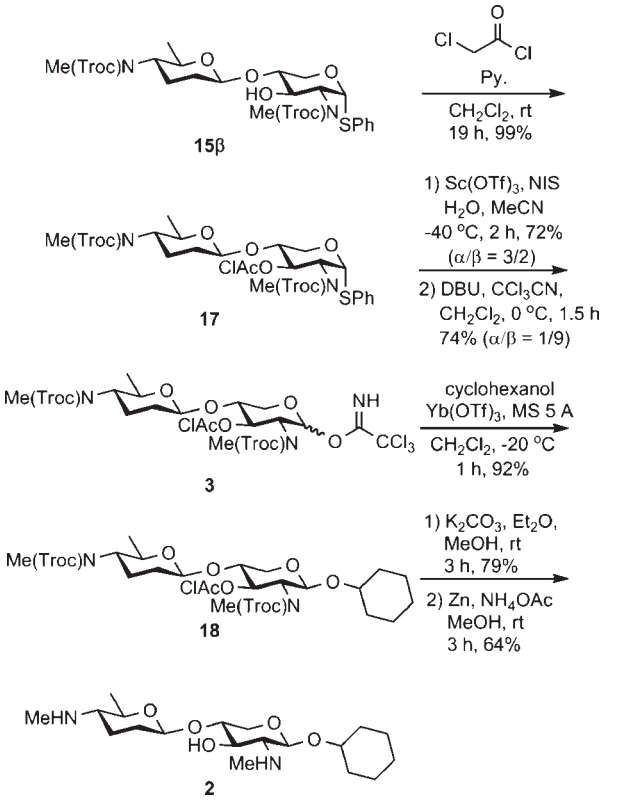
increasing the reaction temperature to −20 °C. These results clearly suggested that the remote participation effect of the *N*-Troc group at the C-4 position was sufficient for highly stereoselective construction of the *N*-monodemethyl-*β*-D-forosaminide bond.

Scheme 3. Completion of the Synthesis of **2**



The completion of the synthesis of **2** is summarized in Scheme 3. Protection of the hydroxy group at the C-3 position of **15*β*** as a chloroacetate gave thioglycoside **17**. Hydrolysis of the thiophenyl group using $Sc(OTf)_3$ and NIS afforded the corresponding lactol without cleavage of the *N*-monodemethyl-*β*-D-forosaminide bond, and subsequent trichloroacetimidate formation provided the key disaccharide donor **3** by treatment with a catalytic amount of DBU and trichloroacetonitril. Next, glycosylation of cyclohexanol (1.0 equiv) as a model aglycon with the resulting glycosyl donor **3** (1.5 equiv) was conducted using $Yb(OTf)_3$ as a mild Lewis acid promoter in CH_2Cl_2 at −20 °C. In this way, the desired *β*-glycoside **18** was obtained in 92% yield as the sole product without anomerization of the preinstalled 2,3,4,6-tetradeoxy-4-methylamino-*β*-glycoside bond. Finally, cleavage of the chloroacetyl group and subsequent deprotection of the *N*-Troc groups using Zn and NH_4OAc in MeOH accomplished the synthesis of the target disaccharide fragment **2**.

In conclusion, the disaccharide fragment **2** of incednine (**1**) was efficiently and stereoselectively synthesized starting from D-xylose and methyl α-D-glucopyranoside (**12**). Stereoselective construction of the *N*-monodemethyl-*β*-D-forosaminide bond was achieved via remote participation-assisted glycosylation using an *N*-Troc group at the C-4 position. Additional studies on the total synthesis of incednine (**1**) using the disaccharide glycosyl donor **3** are currently underway in our laboratory.

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