

## **$\alpha$ -L-VANCOSAMINE ARYL C-GLYCOSIDES, LESS STABLE ANOMERS: A PROBLEM IN SYNTHESIS OF PLURAMYCIN-CLASS ANTIBIOTICS**

**Yoshio Ando,<sup>1</sup> Hiromune Asahina,<sup>1</sup> Kei Kitamura,<sup>1,2</sup> Takashi Matsumoto,<sup>1,3</sup> and Keisuke Suzuki<sup>1\*</sup>**

<sup>1</sup>Department of Chemistry, Tokyo Institute of Technology, 2-12-1 O-okayama, Meguro-ku, Tokyo 152-8551, Japan. <sup>2</sup>Present address: Faculty of Pharmaceutical Sciences, Tokushima Bunri University, 180 Nishihama Yamashiro-cho, Tokushima 770-8514, Japan. <sup>3</sup>Present address: School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

e-mail: ksuzuki@chem.titech.ac.jp

*Dedicated to Professor Kaoru Fuji on occasion of his 80th birthday*

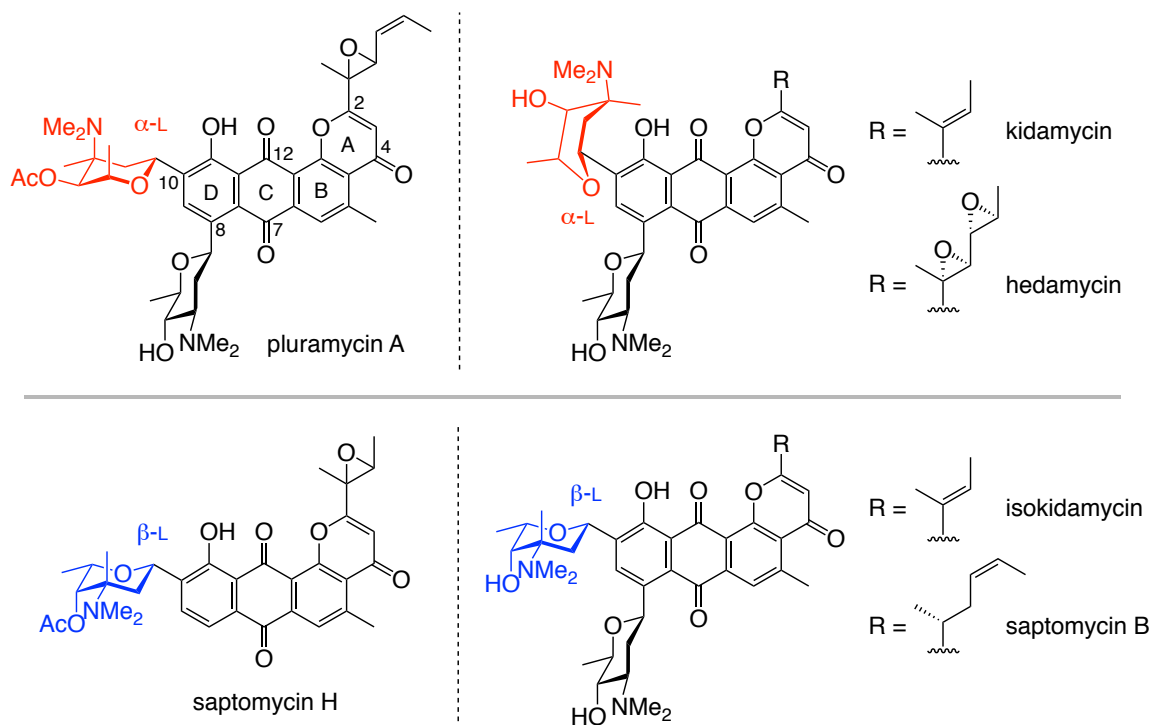
**Abstract** – The pluramycin-class antibiotics have attracted considerable synthetic interest by their bioactivities and unique chemical structures. By the thermodynamic disadvantage, the selective formation of the aryl  $\alpha$ -C-glycoside of an L-vancosamine motif, commonly embedded in this class of natural products, has been one of the problems in their total synthesis. This paper summarizes the stereochemical behavior of the pluramycin-class natural products and reports the results of our model study to address this issue by examining three L-vancosaminyl donors under Lewis acidic conditions.

### **INTRODUCTION**

The pluramycin-class antibiotics have attracted considerable synthetic interest by their bioactivities and unique chemical structures. Pluramycin A, the first member of this class, was discovered as an antitumor antibiotic from *Streptomyces pluricolorescens* by Umezawa and Kondo in 1956.<sup>1,2</sup> Although many congeners were isolated in the following years, their structure elucidation waited for the reports of Iitaka and Furukawa on the chemical derivations, spectroscopic studies, and X-ray diffraction analysis of kidamycin, as its ammonium derivative, revealing an unusual structure feature shared by this class of

natural products, *i.e.* a pyranoanthraquinone core having one or two *C*-glycosides of rare deoxyamino sugars.<sup>3</sup> The X-ray diffraction analysis of a bromobenzoate derivative clarified the absolute stereochemistry, assigning the constituent sugars as D-angolosamine at C8 and *N,N*-dimethyl-L-vancosamine at C10 (Figure 1). This report paved the way for subsequent structure determinations of the related compounds, including pluramycin A,<sup>1</sup> hedamycin,<sup>4</sup> and the saptomycins (Figure 1).<sup>5</sup> The Séquin report on the structure of hedamycin in 1977<sup>4a</sup> is another milestone, comparing the NMR data of hedamycin with those of kidamycin, and also succeeding in the X-ray diffraction analysis of the parent compound to clarify the entire stereochemistry including the bis-oxiranyl side chain. Later it was reported that the two amino sugars play key roles for the sequence selectivity in DNA intercalation, that is the origin of the biological activity.<sup>6</sup>

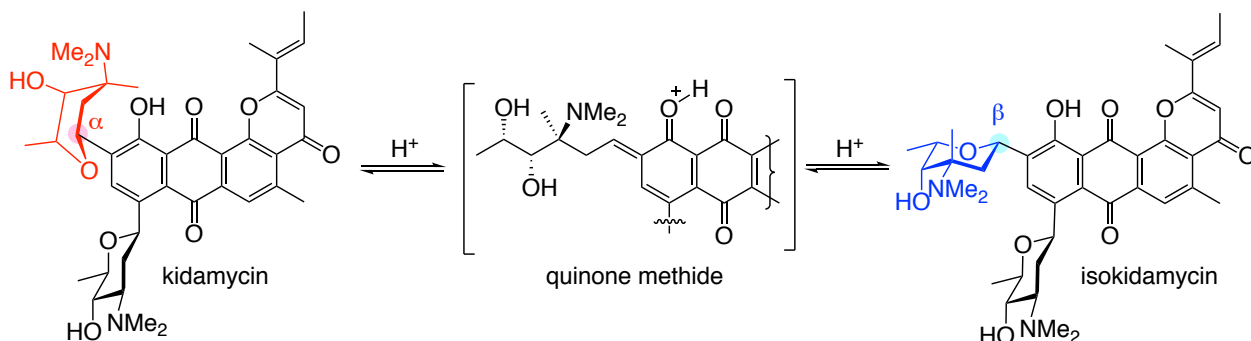
Their structure diversity comes from two main variables. One variable resides in the side chain moiety, differing in the carbon-atom numbers, 4 or 6, and in the presence/absence of oxirane(s). Another variable is the  $\alpha$  or  $\beta$  anomeric stereochemistry of the *N,N*-dimethyl-L-vancosamine *C*-glycosides attached at C10. The  $\alpha$ -L-anomer (red) is involved in pluramycin A, kidamycin and hedamycin, while the  $\beta$ -L-anomer (blue) is seen in saptomycin H, isokidamycin and saptomycin B.<sup>7</sup> There is a reported tendency that the  $\alpha$ -L-anomers show generally higher bioactivity than the corresponding  $\beta$ -L-isomers.<sup>3f,8</sup>



**Figure 1.** The pluramycins

Concerning the thermodynamic preference of these anomers, Iitaka observed an anomerization of kidamycin at its  $\alpha$ -*C*-L-vancosamine moiety by acid treatment, giving the  $\beta$ -anomer, isokidamycin as an

artifact (Scheme 1).<sup>3e,f</sup> Intermediacy of a benzylic cation was proposed to explain this process, and the direction of the isomerization,  $\alpha \rightarrow \beta$ , indicated that the  $\alpha$ -anomer is thermodynamically less stable than the  $\beta$ -anomer.<sup>9</sup>



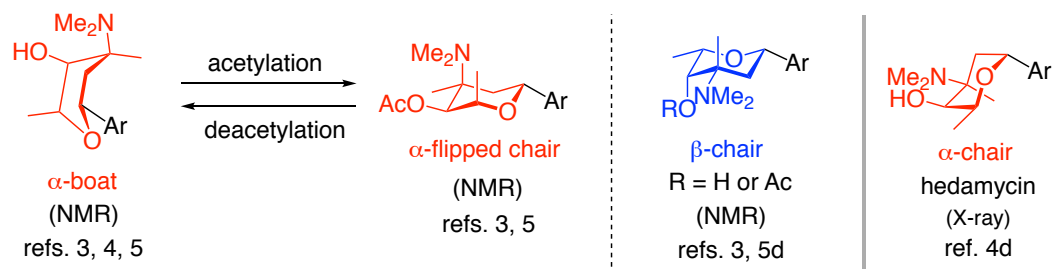
**Scheme 1.** Acid lability of  $\alpha$ -*C*-vancosaminide

*Conformation* Because vancosamine is a branched sugar, the conformational behavior of its *C*-glycosides is not necessarily obvious and worth noting—*various conformers are possible*. Table 1 compiles the reports on the conformations of  $\alpha$ - and  $\beta$ -*C*-glycosides of *N,N*-dimethyl-*L*-vancosamine in a chronological order.

Based on the X-ray data by Iitaka, revealing a boat-like conformation of a kidamycin derivative,<sup>3</sup> the solution conformations of the  $\alpha$ -*L*-vancosamine *C*-glycosides were addressed by NMR spectroscopy, showing that boat-like conformers of kidamycin and hedamycin are prevailing in solution as well. Interestingly, Séquin and Furukawa noted an NMR spectral change upon *acetylation* of kidamycin,<sup>4c</sup> pointing out that a drastic conformational change may be occurring. Abe attributed this spectral change to a boat  $\rightarrow$  flipped chair conformational change, and *vice versa*, they observed a reversed NMR spectral change, upon *deacetylation* of saptomycin D,<sup>5</sup> that was correlated to a reverse conformational change, flipped chair  $\rightarrow$  boat. Note that the conformation of pluramycin A in Figure 1 is arbitrarily drawn as such, as the natural products is an acetate, and the NMR data is consistent with this view.

On the other hand, the  $\beta$ -*L*-anomers invariably take a chair form, whether or not the C4-hydroxy group is acetylated.<sup>3e,f,5d</sup> The Iitaka report on the X-ray data of an isokidamycin derivative<sup>3e</sup> served as a leading reference on the chair conformation of the  $\beta$ -*L*-anomers.

To sum up, the bottom line in the conformation of *L*-vancosamine *C*-glycosides is that the aryl group takes the equatorial disposition for both  $\alpha$  and  $\beta$  anomers, as will be discussed later from a general viewpoint. It is interesting to note an exceptional example, *i.e.*, the X-ray diffraction analysis of hedamycin showed a chair conformation, disposing the aryl group axial!<sup>4d</sup> Séquin remarked this observation as “astounding”, but also noted that this striking data would not affect the above-stated discussion on the solution conformations, with which the present authors agree as well.

**Table 1.** Reports on the conformation of *N,N*-dimethyl-*L*-vancosamine *C*-glycosides

year	compound	$\alpha$ or $\beta$	conformation	basis	refs
1973	kidamycin derivative triacetylmethoxy, bis(methylammonium iodide)	$\alpha$	boat	X-ray	3b
1974	Isokidamycin derivatives bis-( <i>m</i> -Br- and <i>m</i> -I-benzoate)	$\beta$	chair	X-ray	3e
1975	kidamycin	$\alpha$	boat	NMR	3f
	isokidamycin	$\beta$	chair	NMR	3f
1978	hedamycin	$\alpha$	boat	NMR	4b,c
1979	hedamycin	$\alpha$	chair	X-ray	4d
1991	saptomycins D, E	$\alpha$	flipped chair	NMR	5a
1993	saptomycins D, E	$\alpha$	flipped chair	NMR	5b
	→ deacetylsaptomycins D, E	$\alpha$	→ boat	NMR	5b
	saptomycins C <sub>2</sub> , G	$\alpha$	flipped chair	NMR	5d
	saptomycin C <sub>1</sub>	$\alpha$	boat	NMR	5d
	saptomycins B, H	$\beta$	chair	NMR	5d

**Synthesis** Their intriguing structures and significant bioactivities have prompted many endeavors toward their total synthesis, which, however, met with formidable challenges posed by the functional and stereochemical complexity.<sup>10,11</sup> The major synthetic issues include, 1) construction of the highly oxygenated tetracyclic core,<sup>12</sup> 2) regio- and stereoselective installation of the *C*-glycosides. By the need of solving these problems in a coherent manner, only two total syntheses have been recorded to date, including those of isokidamycin by Martin<sup>13</sup> and saptomycin B by our group.<sup>14</sup>

In the issues of installing *C*-glycosides, a particularly difficult problem is the  $\alpha$ -selective formation of the *L*-vancosamine *C*-glycoside, which is less stable than the corresponding  $\beta$ -anomer as discussed before. This aspect is reflected to the relative difficulty of the stereocontrol of the  $\alpha$ -series and the  $\beta$ -series. While access to the  $\beta$ -*C*-glycosides has been well established and exploited in total syntheses,<sup>9,10</sup> no effective approaches has been found to the  $\alpha$ -anomers hampered by the thermodynamic disadvantage. Note that the reactions for the aryl *C*-glycoside synthesis often employ Lewis acidic conditions, which may induce an equilibration between the anomers. Even when the desired anomer was obtained at a certain stage, one needs to be always careful for the potential risk of anomerization. Due to the necessity to avoid acidic

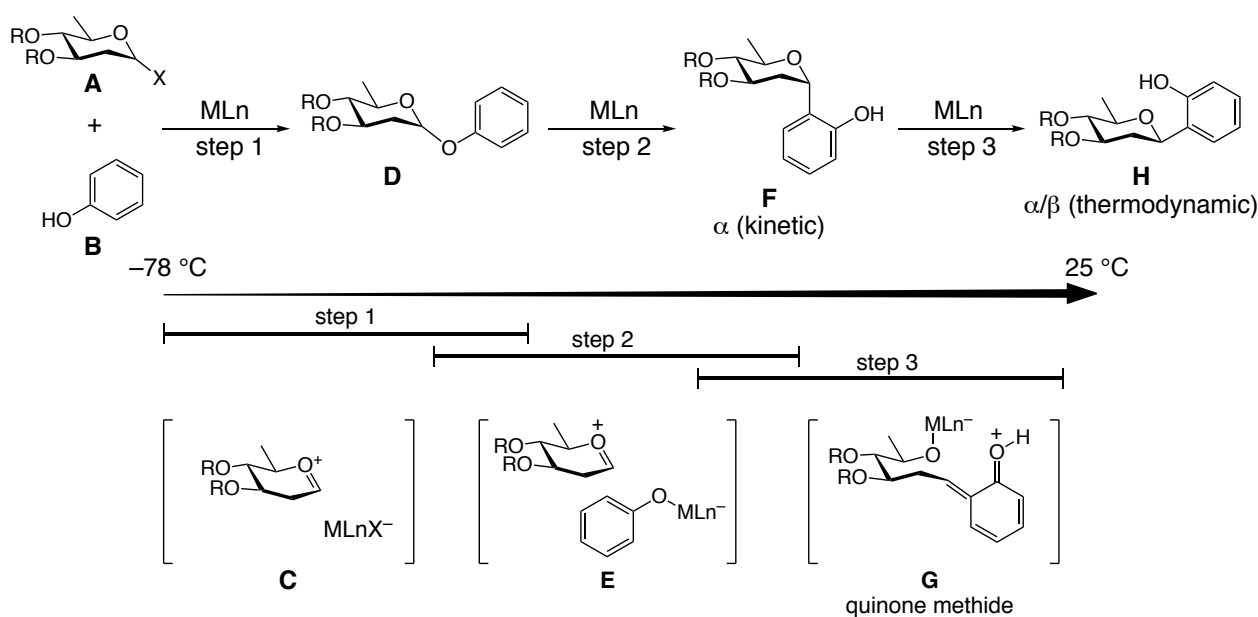
conditions, choice of the synthetic routes is limited all over to the final target.

*O*→*C*-Glycoside rearrangement In our long-standing interest in the total synthesis of aryl *C*-glycoside antibiotics, we previously developed a versatile reaction, “*O*→*C*-glycoside rearrangement”, which is comprised of three Lewis acid-mediated steps.<sup>16</sup> Scheme 2 is a rough picture of the reaction, *i.e.* the time course starting at low temperature in the presence of Lewis acid. As an illustrating example, the *C*-glycosidation of D-olivose derivative is outlined in the following.

*Step 1:* Activation of glycosyl donor **A** at low temperature such as  $-78\text{ }^{\circ}\text{C}$  by a Lewis acid generates an oxonium species **C**, which is intercepted by phenol **B**, giving *O*-glycoside **D**. This step generally completes at low temperature.

*Step 2:* During gradual warming, *O*-glycoside **D** is activated in situ by a Lewis acid, generating an oxonium–phenolate ion pair **E**. This ionization is reversible, but when recapture occurs at the *ortho*-position of the phenol(ate), a C–C bond is formed to give *C*-glycoside **F** irreversibly. A crossover experiment showed that the ion pair is fairly apart in nature, so that the attack of phenolate and/or phenol occurs. We assume here the kinetically favorable pathway is an axial attack to give the  $\alpha$ -anomer, a general trend that was pointed out pioneeringly by Kishi on the stereoelectronic ground.<sup>15</sup>

*Step 3:* An additional event is the stereo-mutation of the kinetically-formed *C*-glycoside **F** into the thermodynamic one **H**,  $\beta$ -*C*-glycosides, which occurs via quinone methide **G** generated by a Lewis acid. An annoying issue to the stereocontrol is that step 3 comes into play before the completion of step 2, thereby sacrificing the kinetically-formed  $\alpha$ -anomer to produce the  $\beta$ -anomer.

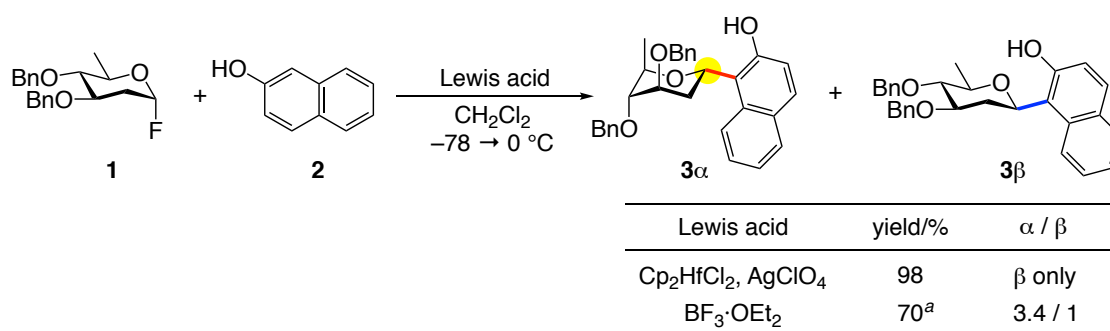


**Scheme 2.** *O*→*C*-glycoside rearrangement

The results are highly dependent on the Lewis acid and also on other reaction parameters. Scheme 3 shows a telling example in the *O*→*C*-glycoside rearrangement of D-olivosyl fluoride **1** with  $\beta$ -naphthol

( $-78\text{ }^{\circ}\text{C} \rightarrow 0\text{ }^{\circ}\text{C}$ ). Two Lewis acids,  $\text{Cp}_2\text{HfCl}_2\text{-AgClO}_4$  and  $\text{BF}_3\cdot\text{OEt}_2$ , gave remarkably different results (the yield and the stereochemical outcome).<sup>16</sup> With  $\text{Cp}_2\text{HfCl}_2\text{-AgClO}_4$ , the  $\beta$ -*C*-glycoside is obtained as a sole product in an excellent yield, whereas, with  $\text{BF}_3\cdot\text{OEt}_2$ , the *O*→*C*-glycoside rearrangement is incomplete, but importantly, the product is rich in the  $\alpha$ -anomer.

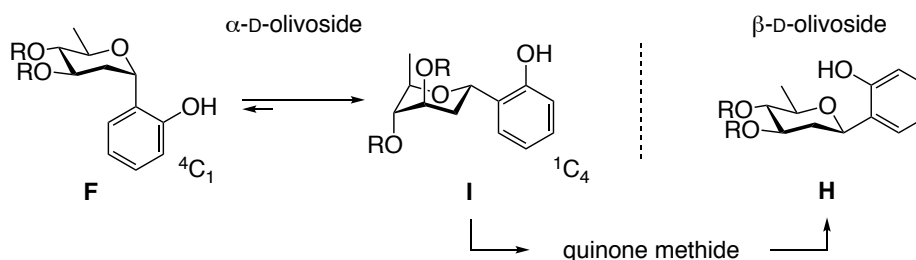
A simple interpretation is that  $\text{Cp}_2\text{HfCl}_2\text{-AgClO}_4$  is a strong Lewis acid that is able to drive both steps 2 and 3 to completion. By contrast,  $\text{BF}_3\cdot\text{OEt}_2$  is a weak Lewis acid, so that both steps 2 and 3 were incomplete, and part of the *O*-glycoside remained unchanged, at least at  $0\text{ }^{\circ}\text{C}$ . Importantly, however, the product was rich in the  $\alpha$ -anomer. This is quite a simplistic view, ignoring other potential relevant factors that may be involved, such as solvent effect and coordination effect of Lewis acid.



a. The corresponding *O*-glycoside was obtained in 28% yield ( $\alpha/\beta = 4.6/1$ ).

**Scheme 3.** Effect of Lewis acid on the *O*→*C*-glycoside rearrangement

It should be noted that  $\alpha$ -anomer **3 $\alpha$**  adopts a  ${}^1\text{C}_4$  conformation **I**, in which the large aryl group occupies an equatorial site by forcing other three substituents axial (Scheme 4). Note that the A-value a phenyl group is 2.8 kcal/mol ( $-100\text{ }^{\circ}\text{C}$ ). A postulate is that  $\alpha$ -*C*-anomer **3 $\alpha$**  is kinetically formed by an axial attack, which was followed by an immediate conformation change,  ${}^4\text{C}_1$ -conformer **F** to  ${}^1\text{C}_4$ -conformer **I**. This is a *pseudo*-stable state, unless exposed to a strong Lewis acid. Upon exposure, Lewis acid would induce anomerization via a quinone methide to the  $\beta$ -anomer **H** that is by far thermodynamically stable than **I**. Note that all four substituents on the pyran ring in **H** are equatorial.



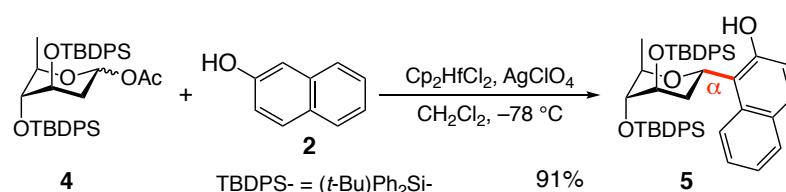
**Scheme 4.** Hints from our early study #1

*Two ideas for the stereoselective  $\alpha$ -C-glycosidation* Implications from these results provided us with the following ideas for the stereocontrol by exploiting  $O \rightarrow C$ -glycoside rearrangement.

Idea #1 (screening of Lewis acids): If one found a Lewis acid that promotes steps 1 and 2, but not step 3, the  $\alpha$ -C-glycoside would be obtained. Desirably, we need a Lewis acid that effects the axial attack (step 2), but not too strong to open the way to the anomerization (step 3).

Idea #2 (substrate design): By a suitable design of substrate, one may have a good chance to render the  ${}^1C_4$ - $\alpha$  conformer thermodynamically preferred.

Concerning the latter idea, we had a remarkable experience as shown in Scheme 5. Note that the C3- and C4-hydroxy groups in **4** were protected as *t*-butyldiphenylsilyl ethers, and the donor **4** already adopted a flipped conformation.<sup>17</sup> The *C*-glycosidation with 2-naphthol exclusively gave the  $\alpha$ -C-D-glycoside **5**, which did not undergo anomerization even after prolonged exposure to strong Lewis acid at ambient temperature, suggesting that the  $\alpha$ -anomer is favored in kinetic and thermodynamic senses.



**Scheme 5.** Hints from our early study #2

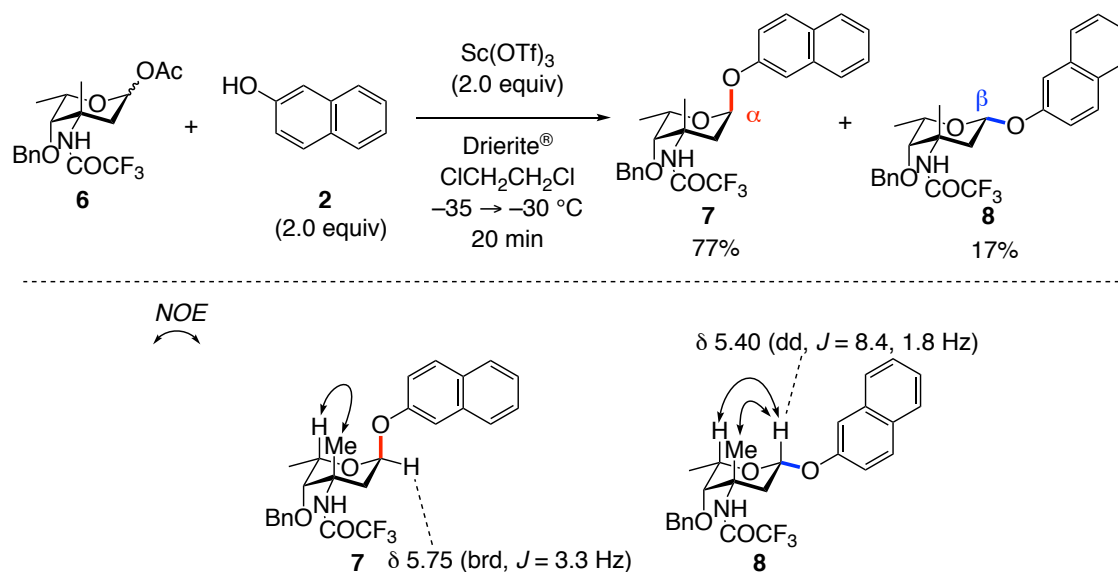
Few examples of the stereoselective construction of less stable anomer of *C*-glycosides have been reported.<sup>16-19</sup> The studies using L-vancosamine derivatives are even rare,<sup>20</sup> as the preparation of the substrates in sufficient amounts is difficult. As we previously established a reliable method of preparing L-vancosamine-related glycosyl donors from methyl  $\alpha$ -D-mannopyranoside,<sup>21</sup> we would position to conduct the present research on the *C*-glycosidation. This paper describes preliminary results on the  $\alpha$ -selective *C*-glycosidation of L-vancosamine.

## RESULTS AND DISCUSSION

We studied the *C*-glycosidation of three L-vancosaminyl donors, **6**, **11** and **19**, with  $\beta$ -naphthol (**2**) as a nucleophilic reaction partner in the presence of Lewis acids. In the following, the ideas behind the design of these donors will be noted and the results of the trials along these lines will be described.

*L*-Vancosaminyl donor **6**<sup>21</sup> The reactivity of donor **6** was examined by using  $Sc(OTf)_3$  as a Lewis acid

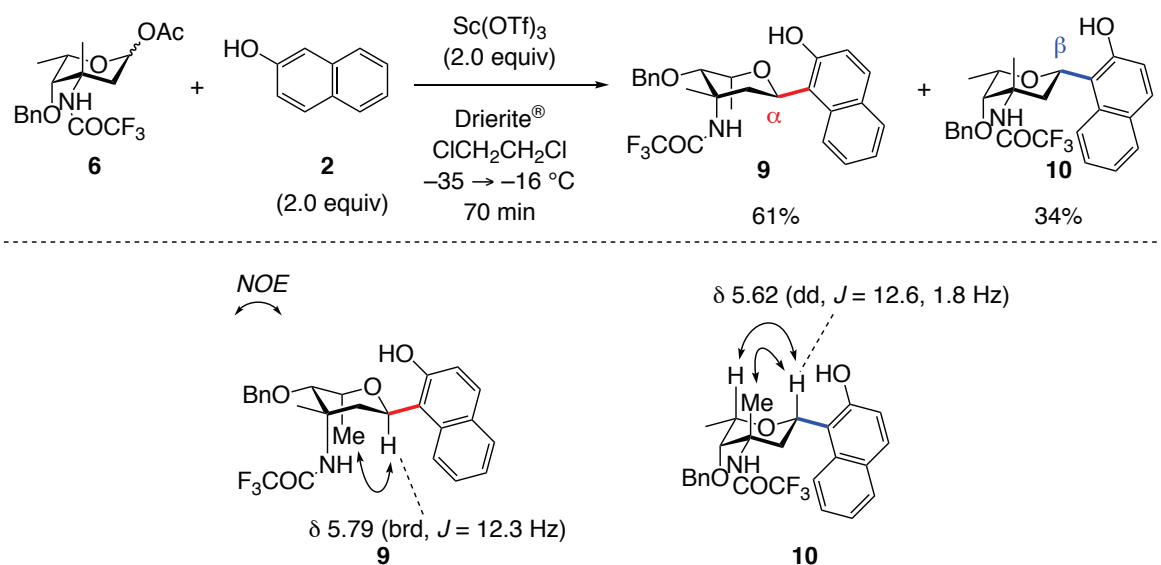
(Scheme 6).<sup>22</sup> A stirred mixture of Sc(OTf)<sub>3</sub> (2.0 equiv.), acceptor **2** (2.0 equiv.) and Drierite<sup>®</sup> in 1,2-dichloroethane was chilled to -35 °C, to which was added donor **6**. Upon gradual warming to -30 °C in 20 min, TLC-monitoring showed the complete consumption of donor **6** and formation of two new compounds [**7**: R<sub>f</sub> = 0.49, **8**: R<sub>f</sub> = 0.42 (hexane, CH<sub>2</sub>Cl<sub>2</sub>, EtOAc = 10/4/1)]. Workup and purification gave  $\alpha$ -*O*-glycoside **7** in 77% yield and  $\beta$ -*O*-glycoside **8** in 17% yield, respectively. The structures were identified by extensive NOE correlations and the coupling constants of the anomeric hydrogen.



**Scheme 6.** *O*-Glycosidation

The above-stated reaction was repeated under the same conditions, but this time, the temperature was raised to -16 °C. The TLC-monitoring suggested complete consumption of **7** and **8**, and formation of two new compounds [**9**: R<sub>f</sub> = 0.46, **10**: R<sub>f</sub> = 0.39 (hexane, CH<sub>2</sub>Cl<sub>2</sub>, EtOAc = 10/4/1)] (Scheme 7). Isolation gave  $\alpha$ -*C*-glycoside **9** in 61% yield and  $\beta$ -*C*-glycoside **10** in 34% yield ( $\alpha$ : $\beta$  = 1.8:1). This result shows that the initially-formed *O*-glycosides **7** and **8** were converted in situ to the corresponding *C*-glycosides **9** and **10** during the gradual warming (*O*→*C*-glycoside rearrangement). Note that the pyran ring in  $\alpha$ -*C*-L-glycoside **9** was flipped (<sup>4</sup>C<sub>1</sub> form), as verified by NOE correlations and coupling constants.





**Scheme 7.** C-Glycosidation

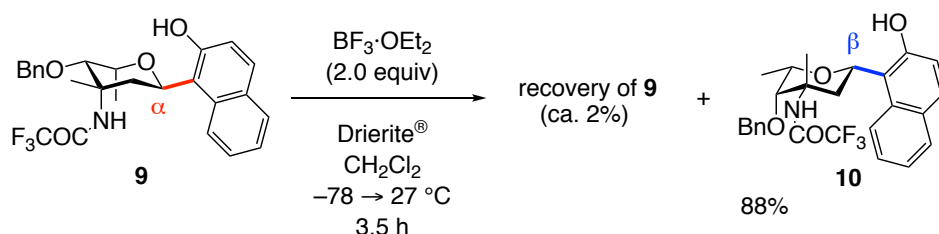
Having identified both anomers of the desired C-glycoside, **9** and **10**, we further examined the effect of Lewis acid (Table 2). When  $\text{BF}_3 \cdot \text{OEt}_2$  was used ( $-35 \rightarrow -15$  °C), the  $\alpha$ -selectivity was slightly improved (entry 1), while TMSOTf led to a  $\beta$ -selective reaction (entry 2). The combination of  $\text{Cp}_2\text{HfCl}_2$  and AgOTf as a Lewis acid required higher temperature for completion of the C-glycoside formation, giving a low selectivity (entry 3). Centering attention to the use of  $\text{BF}_3 \cdot \text{OEt}_2$ , we examined to lower the reaction temperature. For this purpose,  $\text{CH}_2\text{Cl}_2$  was used as the solvent, and the reaction was initiated at  $-78$  °C, where the O-glycoside formation was complete. Subsequent gradual warming to  $-25$  °C gave a high yield of C-glycoside in a high  $\alpha$ -selectivity ( $\alpha:\beta = 5.1:1$ , entry 4). Isolation gave  $\alpha$ -C-glycoside **9** in 77% yield along with the corresponding  $\beta$ -C-glycoside **10** in 15% yield.

**Table 2.** C-Glycosidation of L-vancosaminyl donor **6**

entry	Lewis acid	temp. [°C]	time [min]	<b>9</b> [%]	<b>10</b> [%]	ratio ( $\alpha:\beta$ )
1	$\text{BF}_3 \cdot \text{OEt}_2$	$-35 \rightarrow -15$	40	76	23	3.3:1
2	TMSOTf	$-35 \rightarrow -25$	15	20	62	1:3.1
3	$\text{Cp}_2\text{HfCl}_2$ , AgOTf	$-35 \rightarrow 0$	80	66	32	2.1:1
4 <sup>a</sup>	$\text{BF}_3 \cdot \text{OEt}_2$	$-78 \rightarrow -25$	120	77	15	5.1:1

<sup>a</sup> $\text{CH}_2\text{Cl}_2$  was used as the solvent.

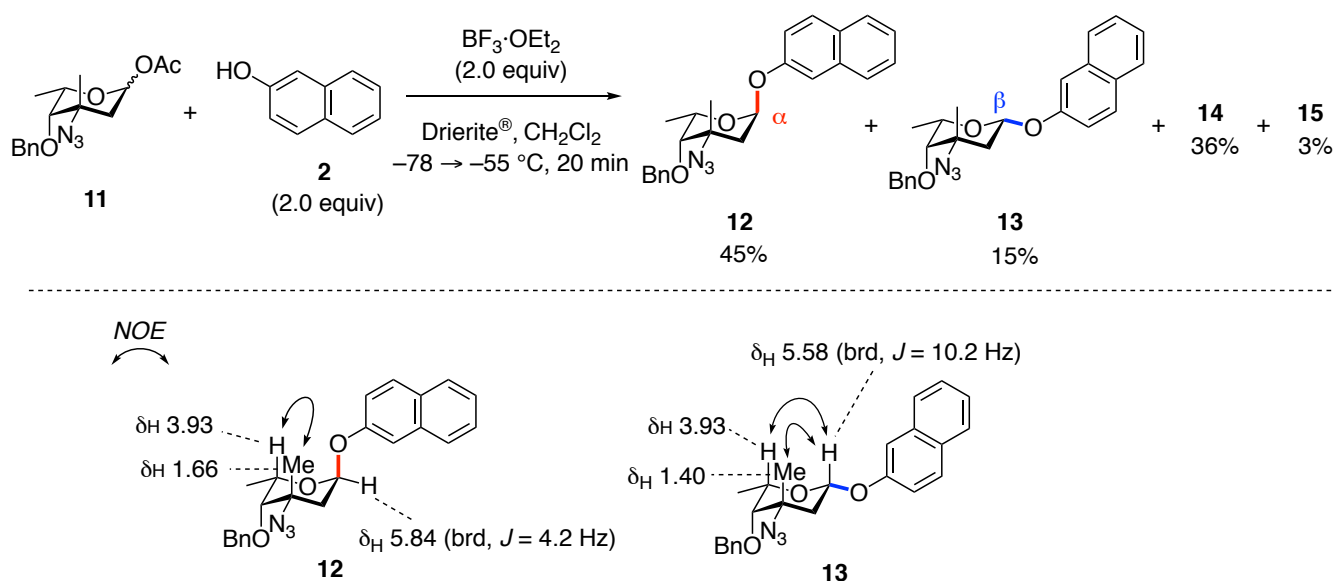
It was confirmed that  $\alpha$ -C-glycoside **9** easily isomerized into the thermodynamically more stable  $\beta$ -C-glycoside **10** in 88% yield under Lewis acidic conditions ( $\text{BF}_3 \cdot \text{OEt}_2$ , 2 equiv.  $-78^\circ\text{C} \rightarrow 27^\circ\text{C}$ , 3.5 h) (Scheme 8). Thus, the  $\alpha$ -L-anomer **9** is the kinetic product, which underwent almost complete anomerization into  $\beta$ -L-anomer **10** by the exposure to Lewis acid at higher temperature.



**Scheme 8.** Anomerization of  $\alpha$ -C-glycoside **9**

*Azido-bearing donor 11*<sup>21</sup> We centered our attention on the azido vancosaminyl donor **11**<sup>21</sup> with a hope that an azido substituent with an unusually small A value (= 0.45 kcal/mol,  $-183^\circ\text{C}$ )<sup>23</sup> would make the  $^4\text{C}_1$  conformation more preferable, thereby increasing the  $\alpha$ -selectivity.

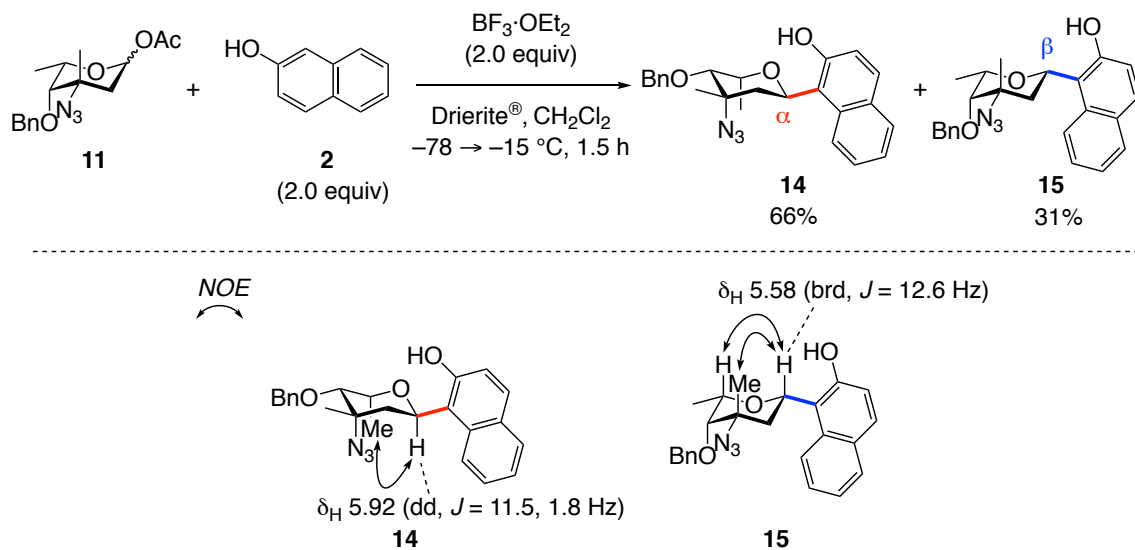
Donor **11** ( $^1\text{C}_4$  form) and  $\beta$ -naphthol (**2**) was treated with  $\text{BF}_3 \cdot \text{OEt}_2$  in  $\text{CH}_2\text{Cl}_2$  at  $-78^\circ\text{C}$ . TLC-Monitoring of the reaction suggested the formation of the *O*-glycosides at low temperature. Upon early quenching at low temperature ( $-78^\circ\text{C} \rightarrow -55^\circ\text{C}$ , 20 min, Scheme 9), the respective  $\alpha$ - and  $\beta$ -*O*-glycosides **12** and **13** were isolated.<sup>24</sup> Already at this stage, partial formation of *C*-glycosides **14** and **15** was noted (vide infra).



**Scheme 9.** *O*-Glycosides

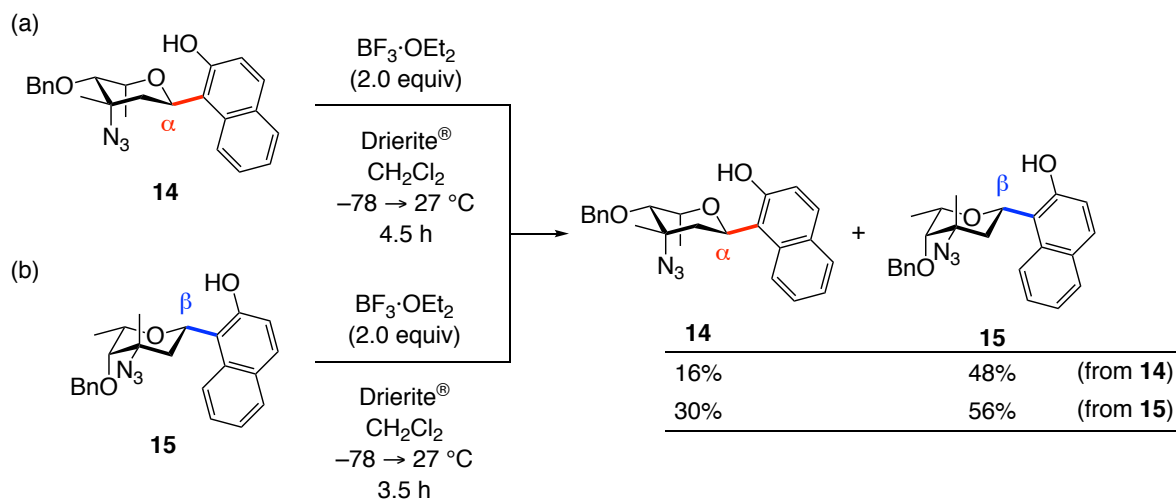
The same reaction was repeated, but this time, the temperature was gradually raised to  $-15^\circ\text{C}$  in 1.5 h, giving  $\alpha$ -*C*-L-glycoside **14** in 66% yield and  $\beta$ -*C*-L-glycoside **15** in 31% yield, respectively ( $\alpha$ : $\beta$  = 2.1:1)

(Scheme 10). The conformation of  $\alpha$ -L-anomer **14** was  ${}^4C_1$  and that of  $\beta$ -L-anomer **15** was  ${}^1C_4$  as expected, which were assigned by extensive NMR studies. The early quenching resulted in high  $\alpha$ -selectivity ( $\alpha$ : $\beta$  = 12/1), albeit low yield (Scheme 9).



**Scheme 10.** C-Glycosidation of azido donor **11**

Upon extended exposure to  $\text{BF}_3 \cdot \text{OEt}_2$  (2.0 equiv.  $-78$  °C  $\rightarrow$   $27$  °C, 4.5 h),  $\alpha$ -C-L-glycoside **14** underwent anomerization, giving an  $\alpha$ / $\beta$ -mixture of C-glycosides **14** and **15** (16% and 48% yield, respectively, Scheme 11a). Under the same conditions,  $\beta$ -C-L-glycoside **15** also underwent anomerization, giving an  $\alpha$ / $\beta$ -mixture of C-glycosides **14** and **15** (30% and 56% yield, respectively, Scheme 11b).<sup>25</sup> Although the material balance was not good, the results clearly show that  $\alpha$ -L-anomer **14** and  $\beta$ -L-anomer **15** are interconvertible under these conditions, indicating the  $\alpha$ / $\beta$  ratio in equilibrium is roughly 1:2 to 1:3.

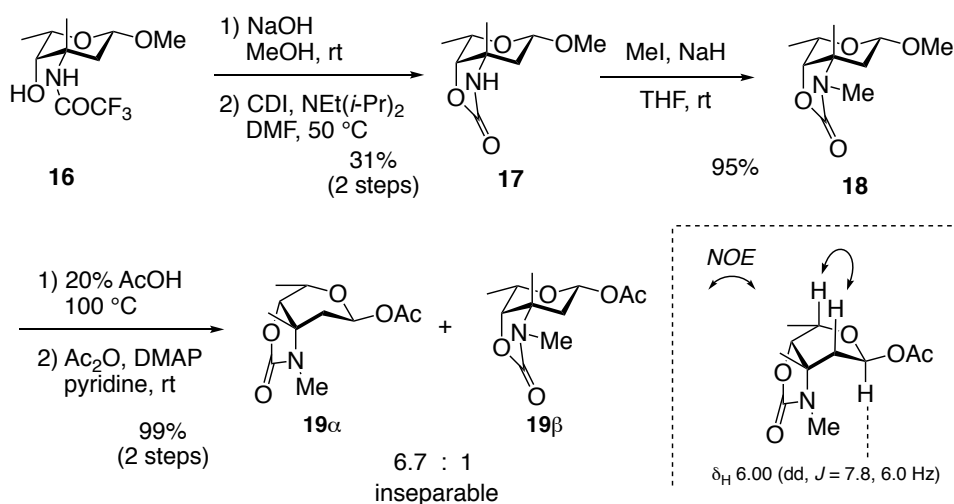


**Scheme 11.** Equilibration of  $\alpha$ -C-glycoside **14** and  $\beta$ -C-glycoside **15**

Our original hope was the small azido substituent would reverse the thermodynamic preference of the  $\alpha$  and  $\beta$  anomers. Although it was not fully realized, the increased proportion of the  $\alpha$ -anomer at equilibrium is a positive, albeit not perfect, answer to our design.

**Bicyclic donor 19** Our next substrate was bicyclic vancosamine donor **19** (Scheme 12), in which the C3 amino and the C4 hydroxy groups were tied as a cyclic carbamate. Based on the conformational constraint offered by a bicyclic system, our hope was the predominant formation of the desired  $\alpha$ -anomer by a convex–concave system of the bicyclic framework.

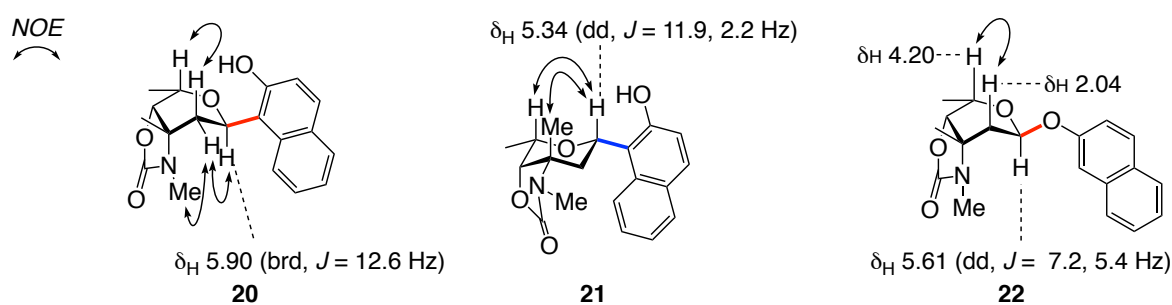
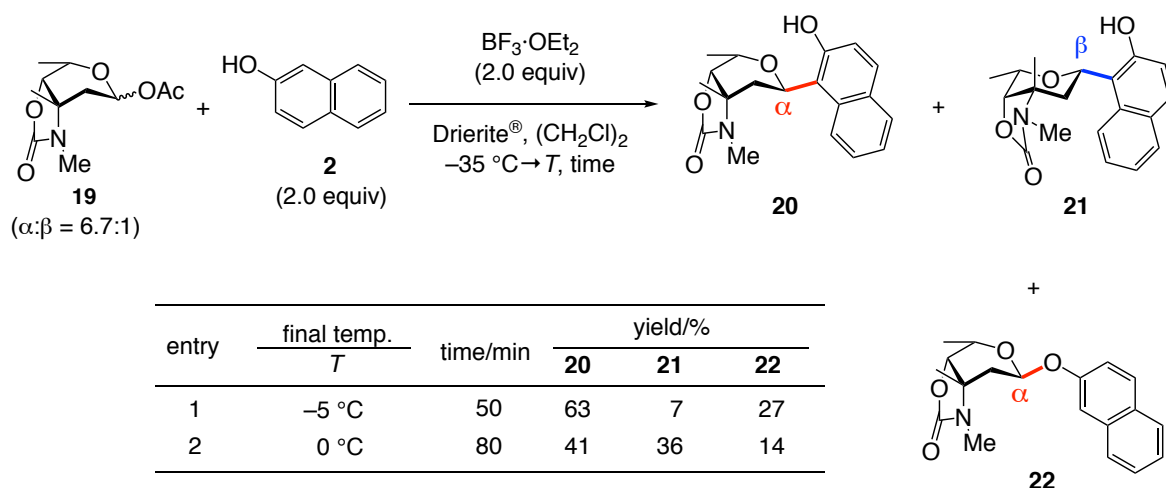
Scheme 12 shows the preparation of bicyclic donor **19** from vancosamine derivative **16**.<sup>21</sup> Basic hydrolysis of the trifluoroacetate **16** followed by treatment with carbonyldiimidazole gave carbamate **17**. After *N*-methylation of **17**, acid hydrolysis of the methyl glycoside moiety and acetylation gave bicyclic donor **19** ( $\alpha:\beta = 6.7:1$ ).<sup>20</sup> Interestingly, the major  $\alpha$ -isomer **19 $\alpha$**  adopted a boat conformation (NMR).<sup>26</sup>



**Scheme 12.** Synthesis of bicyclic donor **19**

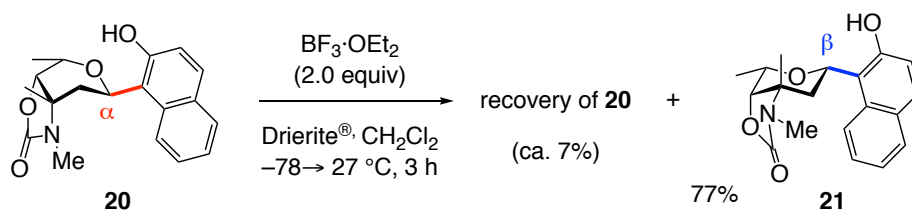
Scheme 13 shows the reaction of bicyclic donor **19**. Upon treatment of donor **19** and 2-naphthol in the presence of  $\text{BF}_3 \cdot \text{OEt}_2$  ( $-35\text{ }^\circ\text{C} \rightarrow -5\text{ }^\circ\text{C}$ , 50 min), the reaction proceeded in an excellent  $\alpha/\beta$  selectivity, giving  $\alpha$ -L-C-glycoside **20** in 63% yield and  $\beta$ -L-C-glycoside **21** in 7% yield (entry 1). Thus, donor **19** is a promising substrate to realize the projected stereoselective C-glycosidation ( $\alpha:\beta = 9/1$ ). An additional point to note here was that the  $O \rightarrow C$  rearrangement was incomplete, as the O-glycoside **22** (only  $\alpha$ -anomer) was obtained in 27% yield. The structures of **20**, **21**, and **22** were assigned by extensive NMR studies.

For driving the  $O \rightarrow C$  rearrangement step to completion, the same reaction was repeated by setting a slightly higher final temperature,  $0\text{ }^\circ\text{C}$  (entry 2). Surprisingly, such a small change gave a much poorer  $\alpha/\beta$  selectivity (1.1:1), while O-glycoside **22** still remained.



**Scheme 13.** C-Glycosidation of bicyclic donor **19**

This remarkable result suggested that the emergence of the anomerization step, and the thermodynamic preference of the  $\beta$ -anomer **21** over the  $\alpha$ -anomer **20**. Indeed, an equilibration experiment by prolonged treatment of **20** with  $\text{BF}_3 \cdot \text{OEt}_2$  ( $-78\text{ }^\circ\text{C} \rightarrow 27\text{ }^\circ\text{C}$ , 3 h) gave a highly  $\beta$ -rich mixture of anomers ( $\alpha/\beta = 1/11$ , Scheme 14).



**Scheme 14.** Equilibration of  $\alpha$ -C-glycoside **20** and  $\beta$ -anomer **21**

Two implications learned from these experiments are as follows.

- (1) *Kinetic control*: The high stereoselectivity, **20** > **21** shown in entry 1 (Scheme 13), is reflecting the high kinetic facial selection explained by the convex–concave terms. The bicyclic oxonium species involved (not shown) undergoes a nucleophilic attack from its *convex* face,<sup>9a</sup> which also accounts for the high  $\alpha$ -anomer proportion in O-glycosides **22** and acetate **19** ( $\alpha/\beta = 6.7/1$ ). Thus, the idea using a cyclic carbamate for the projected stereocontrol proved to be effective.

(2) *Thermodynamic control*: The origin of the thermodynamic preference, **20** < **21** (Scheme 14), could be understood by their conformational analysis (Scheme 13). Based on the NMR analysis, the  $\alpha$ -L-anomer **20** takes a boat conformation, disposing the C1 aryl group equatorial. It was noted that an  $\alpha \rightarrow \beta$  anomerization occurs also in this bicyclic system, and the resulting  $\beta$ -L-anomer **21** acquires thermodynamic stability by adopting a less strained chair conformation.

Thus, a guideline became clear for the selective access to the  $\alpha$ -L-anomer, i.e., to capture the kinetic product **22**. However, only a narrow window is open in this system, because the anomerization step already comes into play at the temperature range around 0 °C.

## CONCLUSIONS

Model studies on the  $\alpha$ -stereoselective aryl *C*-glycosidation of L-vancosamine have been carried out. Three sorts of glycosyl donor were tested for the *O*→*C*-glycoside rearrangement. The stereochemical outcome strongly depended on the structure of glycosyl donor, Lewis acid, and the experimental conditions. In respective three cases examined, the desired  $\alpha$ -L-anomer was a kinetic product, while the  $\beta$ -L-product was thermodynamically favored as revealed by equilibration experiments. Although not fully optimized, these observations would serve as a guideline to develop a selective, robust route to the  $\alpha$ -L-vancosamine *C*-glycoside. A good substrate design as well as precise tuning of the reaction conditions will be needed, which are now actively investigated in our laboratory.

## EXPERIMENTAL

*General*. All reactions using air- or moisture-sensitive reagents were performed in dried glassware under an atmosphere of dry argon. Ethereal solvents (anhydrous; Kanto Chemical Co., Inc.) were used as received by using an Organic Solvent Pure Unit (Wako Pure Chemical Industries Ltd.). Dichloromethane  $\{(\text{CH}_2\text{Cl})_2\}$  and 1,2-dichloroethane ( $\text{CH}_2\text{Cl}_2$ ) were distilled successively from  $\text{P}_2\text{O}_5$  and  $\text{CaH}_2$  and stored over 4A molecular sieves. Other reagents were used without further purification as received from commercial. For thin-layer chromatography (TLC) analysis, Merck pre-coated plates (TLC silica gel 60  $\text{F}_{254}$ , Art 5715, 0.25 mm) were used. Silica-gel preparative thin-layer chromatography (PTLC) was performed using plates prepared from Merck silica gel 60  $\text{PF}_{254}$  (Art 7747). For flash column chromatography, silica gel 60N (Spherical, neutral, 63–210  $\mu\text{m}$ ) from Kanto Chemical was used.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR were measured on a Bruker Avance III 600 (600 MHz) spectrometer in the solvent indicated; Chemical shifts ( $\delta$ ) are expressed in parts per million (ppm) downfield from internal standard {tetramethylsilane (0.00 ppm) or  $\text{CHCl}_3$  (7.26 ppm) for  $\text{CDCl}_3$ }, and coupling constants (*J*) are reported as hertz (Hz). Splitting patterns are indicated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Infrared (IR) spectra and attenuated total reflectance Fourier-transform infrared

(ATR-FTIR) spectra were recorded on Thermo Fisher SCIENTIFIC NICOLET iS5 FTIR spectrometer. Optical rotations ( $[\alpha]_D$ ) were measured on a JASCO DIP-1000 polarimeter. High-resolution mass spectra (HRMS) were obtained with a Bruker micrOTOF-Q II spectrometer (ESI and APCI).

**1-(4-Benzyl-1,2,3,6-tetra-deoxy-3-methyl-3-trifluoroacetyl-amino- $\alpha$ -L-lyxo-hexopyranosyl)-2-naphthol (9) and 1-(4-benzyl-1,2,3,6-tetra-deoxy-3-methyl-3-trifluoroacetyl-amino- $\beta$ -L-lyxo-hexopyranosyl)-2-naphthol (10).** Drierite<sup>®</sup> (232 mg) was placed in 30 mL two-necked, round-bottom flask, and dried by heating with a heat gun under vacuum. After cooling to room temperature, the flask was filled with argon and charged with 2-naphthol (23.0 mg, 0.159 mmol), L-vancosamine acetate **6** (30.0 mg, 77.0  $\mu$ mol) and CH<sub>2</sub>Cl<sub>2</sub> (2.7 mL). To the mixture was added BF<sub>3</sub>·OEt<sub>2</sub> (20  $\mu$ L, 0.16 mmol) at  $-78$  °C, and gradually warmed to  $-25$  °C over 2 h, and then quenched by adding saturated aqueous NaHCO<sub>3</sub>. After filtration through a Celite<sup>®</sup> pad, the products were extracted with EtOAc ( $\times 3$ ), and the combined organic extracts were washed with brine, and dried (Na<sub>2</sub>SO<sub>4</sub>). After filtration, removal of the solvents in vacuo and purification by PTLC (silica gel, hexane, CH<sub>2</sub>Cl<sub>2</sub>, EtOAc = 10/4/1) afforded  $\alpha$ -C-glycoside **9** (28.9 mg, 77%) as a colorless oil and  $\beta$ -C-glycoside **10** (5.8 mg, 15%) as white needles.

**9:**  $R_f$  = 0.46 (hexane, CH<sub>2</sub>Cl<sub>2</sub>, EtOAc = 10/4/1).  $[\alpha]_D^{25} +109$  ( $c$  0.643, CHCl<sub>3</sub>). IR (neat) 3404, 3326, 2989, 2937, 1729, 1623, 1602, 1524, 1470, 1455, 1220, 1173, 1093, 748, 733 cm<sup>-1</sup>. <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): 1.46 (s, 3H), 1.56 (d, 3H,  $J$  = 7.2 Hz), 1.86 (dd, 1H,  $J$  = 15.0, 12.3 Hz), 3.47 (brd, 1H,  $J$  = 15.0 Hz), 3.62 (d, 1H,  $J$  = 6.6 Hz), 4.59 (qd, 1H,  $J$  = 7.2, 6.6 Hz), 4.67 (d, 1H,  $J$  = 12.0 Hz), 4.77 (d, 1H,  $J$  = 12.0 Hz), 5.79 (brd, 1H,  $J$  = 12.3 Hz), 6.88 (brs, 1H, NH), 7.07 (d, 1H,  $J$  = 9.0 Hz), 7.30 (t, 1H,  $J$  = 7.8 Hz), 7.34–7.47 (m, 6H), 7.55 (d, 1H,  $J$  = 8.4 Hz), 7.67 (d, 1H,  $J$  = 9.0 Hz), 7.73 (d, 1H,  $J$  = 7.8 Hz), 8.92 (s, 1H, OH). <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>): 12.4, 24.8, 37.6, 57.0, 66.5, 70.5, 73.2, 78.3, 114.1, 115.7 (q,  $J$ (C,F) = 288 Hz), 119.5, 119.6, 120.8, 123.2, 127.1, 128.1, 128.7, 128.8, 128.9, 130.0, 131.0, 136.5, 153.9, 156.6 (q,  $J$ (C,F) = 36.0 Hz). HR-ESI-MS: 496.1713 ([M+Na]<sup>+</sup>, C<sub>26</sub>H<sub>26</sub>F<sub>3</sub>NNaO<sub>4</sub>; calc. 496.1706).

**10:**  $R_f$  = 0.39 (hexane, CH<sub>2</sub>Cl<sub>2</sub>, EtOAc = 10/4/1). Mp 138.0–139.0 °C.  $[\alpha]_D^{25} -127$  ( $c$  1.67, CHCl<sub>3</sub>). IR (neat) 3314, 3065, 3033, 2985, 2927, 1718, 1623, 1601, 1556, 1524, 1469, 1407, 1351, 1265, 1218, 1160, 1073, 818, 753, 704 cm<sup>-1</sup>. <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): 1.43 (d, 3H,  $J$  = 6.0 Hz), 1.88 (s, 3H), 2.03 (brd, 1H,  $J$  = 12.6 Hz), 2.31 (t, 1H,  $J$  = 12.6 Hz), 3.79 (brs, 1H), 4.09 (brq, 1H,  $J$  = 6.0 Hz), 4.63 (d, 1H,  $J$  = 11.4 Hz), 4.85 (d, 1H,  $J$  = 11.4 Hz), 5.62 (dd, 1H,  $J$  = 12.6, 1.8 Hz), 6.31 (brs, 1H, NH), 7.12 (d, 1H,  $J$  = 9.0 Hz), 7.29–7.41 (m, 6H), 7.45 (t, 1H,  $J$  = 8.4 Hz), 7.62 (d, 1H,  $J$  = 8.4 Hz), 7.68 (d, 1H,  $J$  = 9.0 Hz), 7.75 (d, 1H,  $J$  = 8.4 Hz), 8.83 (s, 1H, OH). <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>): 18.3, 20.4, 36.8, 56.5, 72.6, 72.8, 76.3, 78.9, 115.0, 115.3 (q,  $J$ (C,F) = 287 Hz), 119.8, 120.2, 123.0, 126.9, 127.5, 128.2, 128.6, 128.8, 129.0, 130.1, 130.6, 137.2, 154.3, 156.6 (q,  $J$ (C,F) = 36.0 Hz). HR-ESI-MS: 496.1706 ([M+Na]<sup>+</sup>, C<sub>26</sub>H<sub>26</sub>F<sub>3</sub>NNaO<sub>4</sub>; calc. 496.1706).

**1-(3-Azido-4-benzyl-1,2,3,6-tetra-deoxy-3-methyl- $\alpha$ -L-lyxo-hexopyranosyl)-2-naphthol (14) and**

**1-(3-azido-4-benzyl-1,2,3,6-tetra-deoxy-3-methyl- $\beta$ -L-lyxo-hexopyranosyl)-2-naphthol (15).** Drierite<sup>®</sup> (82 mg) was placed in 20 mL two necked, round-bottom flask, and dried by heating with a heat gun under vacuum. After cooling to room temperature, the flask was filled with argon and charged with 2-naphthol (7.5 mg, 0.052 mmol), L-vancosamine acetate **11** (8.5 mg, 0.027 mmol) and CH<sub>2</sub>Cl<sub>2</sub> (0.9 mL). To the mixture was added BF<sub>3</sub>·OEt<sub>2</sub> (7  $\mu$ L, 0.053 mmol) at -78 °C. The reaction temperature was gradually raised to -15 °C over 1.5 h, and then quenched by adding Et<sub>3</sub>N. After filtration through a Celite<sup>®</sup> pad, the products were extracted with EtOAc ( $\times$ 3), and the combined organic extracts were washed with brine, and dried (Na<sub>2</sub>SO<sub>4</sub>). After filtration, removal of the solvents in vacuo and purification by PTLC (silica gel, hexane, EtOAc = 10/1) gave  $\alpha$ -L-anomer **14** (7.1 mg, 66%) as a colorless oil and  $\beta$ -L-anomer **15** (3.3 mg, 31%) as a colorless oil.

**14:**  $R_f$  = 0.57 (hexane, EtOAc = 3/1).  $[\alpha]_D^{25}$  +93.7 ( $c$  1.54, CHCl<sub>3</sub>). IR (neat) 3403, 3322, 3304, 2988, 2936, 2124, 1728, 1623, 1601, 1524, 1469, 1408, 1329, 1270, 1219, 1172, 1093, 893, 818, 748, 699, 654. <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): 1.47 (s, 3H), 1.70 (d, 3H,  $J$  = 7.2 Hz), 1.86 (dd, 1H,  $J$  = 13.8, 11.4 Hz), 1.99 (brd, 1H,  $J$  = 13.8 Hz), 3.71 (d, 1H,  $J$  = 6.0 Hz), 4.59–4.63 (m, 1H), 4.62 (d, 1H,  $J$  = 12.0 Hz), 4.76 (d, 1H,  $J$  = 12.0 Hz), 5.92 (dd, 1H,  $J$  = 11.5, 1.8 Hz), 7.07 (d, 1H,  $J$  = 9.0 Hz), 7.30–7.35 (m, 2H), 7.39–7.41 (m, 4H) 7.49 (dd, 1H,  $J$  = 8.4, 7.8 Hz), 7.67 (d, 1H,  $J$  = 9.0 Hz); 7.72 (d, 1H,  $J$  = 8.4 Hz), 7.75 (d, 1H,  $J$  = 8.4 Hz), 9.05 (s, 1H, OH). <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>): 12.3, 23.7, 42.7, 61.1, 66.4, 71.5, 72.7, 80.7, 114.4, 119.7, 120.8, 123.0, 126.9, 127.5, 128.0, 128.6, 128.7, 128.8, 129.7, 130.9, 137.4, 154.0. HR-ESI-MS: 426.1814 ([M+Na]<sup>+</sup>, C<sub>24</sub>H<sub>25</sub>N<sub>3</sub>NaO<sub>3</sub>; calc. 426.1788).

**15:**  $R_f$  = 0.46 (hexane, EtOAc = 3/1).  $[\alpha]_D^{25}$  -141 ( $c$  1.77, CHCl<sub>3</sub>). IR (neat) 3320, 2982, 2925, 2099, 1622, 1600, 1468, 1405, 1265, 1229, 1071, 820, 747, 696, 665. <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): 1.30 (d, 3H,  $J$  = 6.0 Hz), 1.57 (s, 3H), 1.85 (brd, 1H,  $J$  = 13.2 Hz), 2.68 (dd, 1H,  $J$  = 13.2, 12.6 Hz), 3.21 (brs, 1H), 3.98 (brq, 1H,  $J$  = 6.0 Hz), 4.69 (d, 1H,  $J$  = 11.4 Hz), 5.06 (d, 1H,  $J$  = 11.4 Hz), 5.58 (brd, 1H,  $J$  = 12.6 Hz), 7.14 (d, 1H,  $J$  = 9.0 Hz), 7.31 (t, 1H,  $J$  = 7.8 Hz), 7.32 (t, 1H,  $J$  = 7.2 Hz), 7.39 (t, 1H,  $J$  = 7.2 Hz), 7.39 (t, 1H,  $J$  = 7.2 Hz), 7.44 (d, 2H,  $J$  = 7.2 Hz), 7.45 (t, 1H,  $J$  = 7.2 Hz), 7.62 (d, 1H,  $J$  = 7.8 Hz), 7.70 (d, 1H,  $J$  = 9.0 Hz), 7.77 (d, 1H,  $J$  = 7.8 Hz), 8.82 (s, 1H, OH). <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>): 17.8, 22.1, 35.0, 62.1, 73.3, 73.4, 75.8, 81.4, 115.2, 120.0, 120.1, 122.8, 126.8, 127.67, 127.74, 128.4, 128.6, 129.0, 129.9, 130.7, 137.8, 154.3. HR-ESI-MS: 426.1788 ([M+Na]<sup>+</sup>, C<sub>24</sub>H<sub>25</sub>N<sub>3</sub>NaO<sub>3</sub>; calc. 426.1788).

**1-(3-*N*,4-*O*-Carbonyl-1,2,3,6-tetra-deoxy-3-methyl-3-*N*-methylamino- $\alpha$ -L-lyxo-hexopyranosyl)-2-naphthol (20), 1-(3-*N*,4-*O*-carbonyl-1,2,3,6-tetra-deoxy-3-methyl-3-*N*-methylamino- $\beta$ -L-lyxo-hexopyranosyl)-2-naphthol (21), and 2-naphthyl 3-*N*,4-*O*-carbonyl-1,2,3,6-tetra-deoxy-3-methyl-3-*N*-methylamino- $\alpha$ -L-lyxo-hexopyranoside (22).** Drierite<sup>®</sup> (114 mg) was placed in 20 mL two necked, round-bottom flask, and dried by heating with a heat gun under vacuum. After cooling to room temperature, the flask was filled with argon and charged with 2-naphthol (11.1 mg, 0.0773 mmol),



L-vancosamyl acetate **19** (9.4 mg, 0.039 mmol) and (CH<sub>2</sub>Cl)<sub>2</sub> (1.3 mL). To the mixture was added BF<sub>3</sub>·OEt<sub>2</sub> (10 μL, 0.081 mmol) at –35 °C. The reaction mixture was stirred and gradually warmed to –5 °C over 50 min, and then quenched by addition of saturated aqueous NaHCO<sub>3</sub>. After filtration through a Celite<sup>®</sup> pad, the products were extracted with EtOAc (×3), and the combined organic extracts were washed with brine, and dried over Na<sub>2</sub>SO<sub>4</sub>. After filtration, removal of the solvents in vacuo and purification by PTLC (silica gel, CH<sub>2</sub>Cl<sub>2</sub>, EtOAc = 10/1) gave α-C-glycoside **20** (15.9 mg, 63%) as a colorless oil and a inseparable mixture of α-O-glycoside **22** and β-C-glycoside **21**. The mixture was further purified by GPC (CHCl<sub>3</sub>) to give α-O-glycoside **22** (6.8 mg, 27%) as white powders and β-C-glycoside **21** (1.8 mg, 7%) as a colorless oil.

**20**: *R*<sub>f</sub> = 0.50 (CH<sub>2</sub>Cl<sub>2</sub>, EtOAc = 3/1). Mp 227.6–228.0 °C. [α]<sub>D</sub><sup>25</sup> +77.5 (*c* 0.977, CHCl<sub>3</sub>). IR (neat) 3315, 2924, 1719, 1436, 1404, 1304, 1143, 1007, 820, 750 cm<sup>-1</sup>. <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): 1.47 (s, 3H), 1.52 (d, 3H, *J* = 6.6 Hz), 2.05 (dd, 1H, *J* = 15.0, 12.6 Hz), 2.13 (brd, 1H, *J* = 15.0 Hz), 2.97 (s, 3H), 4.23 (brs, 1H), 4.42 (brq, 1H, *J* = 6.6 Hz), 5.90 (brd, 1H, *J* = 12.6 Hz), 7.08 (d, 1H, *J* = 9.0 Hz), 7.30–7.32 (m, 1H), 7.43–7.44 (m, 2H), 7.68 (d, 1H, *J* = 9.0 Hz), 7.76 (d, 1H, *J* = 8.4 Hz), 9.15 (s, 1H, OH). <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>): 17.9, 24.6, 25.5, 34.9, 57.9, 66.1, 70.8, 81.2, 114.2, 119.8, 119.9, 123.1, 127.1, 129.0, 129.2, 130.0, 130.6, 154.2, 156.7. HR-ESI-MS: 350.1361 ([M+Na]<sup>+</sup>, C<sub>19</sub>H<sub>21</sub>NNaO<sub>4</sub>; calc. 350.1363).

**21**: *R*<sub>f</sub> = 0.61 (CH<sub>2</sub>Cl<sub>2</sub>, EtOAc = 3/1). [α]<sub>D</sub><sup>25</sup> –184 (*c* 0.706, CHCl<sub>3</sub>). IR (neat) 3342, 2983, 2360, 1752, 1623, 1379, 1259, 1229, 1124, 1053, 1013, 987, 949, 752 cm<sup>-1</sup>. <sup>1</sup>H-NMR (600 MHz, CDCl<sub>3</sub>): 1.57 (d, 3H, *J* = 6.0 Hz), 1.62 (s, 3H), 1.99 (dd, 1H, *J* = 13.8, 12.0 Hz), 2.12 (brd, 1H, *J* = 13.8 Hz), 2.71 (s, 3H), 3.87 (brs, 1H), 4.07 (brq, 1H, *J* = 6.0 Hz), 5.34 (dd, 1H, *J* = 11.9, 2.2 Hz), 7.12 (d, 1H, *J* = 9.0 Hz), 7.33 (dd, 1H, *J* = 7.2, 6.9 Hz), 7.47 (dd, 1H, *J* = 8.1, 6.9 Hz), 7.50 (d, 1H, *J* = 8.1 Hz), 7.70 (d, 1H, *J* = 9.0 Hz), 7.78 (d, 1H, *J* = 7.2 Hz), 8.59 (s, 1H, OH). <sup>13</sup>C-NMR (150 MHz, CDCl<sub>3</sub>): 17.0, 20.8, 25.6, 37.9, 58.5, 72.0, 74.3, 78.5, 113.9, 119.9, 120.2, 123.0, 127.0, 128.7, 129.2, 130.1, 130.4, 153.9, 157.4. HR-ESI-MS: 350.1364 ([M + Na]<sup>+</sup>, C<sub>19</sub>H<sub>21</sub>NNaO<sub>4</sub>; calc. 350.1363).

**22**: *R*<sub>f</sub> = 0.66 (CH<sub>2</sub>Cl<sub>2</sub>, EtOAc = 3/1); [α]<sub>D</sub><sup>25</sup> –68.9 (*c* 0.283, CHCl<sub>3</sub>). IR (ATR) 2972, 2931, 1744, 1634, 1558, 1454, 1380, 1159, 1128, 1066, 990, 736 cm<sup>-1</sup>. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 1.33 (d, 3H, *J* = 6.6 Hz), 1.49 (s, 3H), 2.04 (dd, 1H, *J* = 15.0, 7.2 Hz), 2.30 (dd, 1H, *J* = 15.0, 5.4 Hz), 2.83 (s, 3H), 4.04 (brs, 1H), 4.20 (brq, 1H, *J* = 6.6 Hz), 5.61 (dd, 1H, *J* = 7.2, 5.4 Hz), 7.17 (brd, 1H, *J* = 9.0 Hz), 7.36 (dd, 1H, *J* = 7.8, 7.2 Hz), 7.44–7.46 (m, 2H), 7.75–7.78 (m, 3H). <sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>) δ 15.6, 24.9, 25.6, 33.5, 57.4, 64.7, 80.0, 94.6, 110.7, 118.9, 124.2, 126.5, 127.2, 127.6, 129.4, 129.6, 134.4, 154.5, 157.3. HR-ESI-MS: 350.1366 ([M+Na]<sup>+</sup>, C<sub>19</sub>H<sub>21</sub>NNaO<sub>4</sub>; calc. 350.1363).

## ACKNOWLEDGMENTS

This research was supported by JSPS KAKENHI Grant JP16H06351.

## REFERENCES AND NOTES

1. Pluramycin A: (a) K. Maeda, T. Takeuchi, K. Nitta, K. Yagishita, R. Utahara, T. Osato, M. Ueda, S. Kondo, Y. Okami, and H. Umezawa, *J. Antibiot.*, 1956, **9**, 75; (b) S. Kondo, M. Miyamoto, H. Naganawa, T. Takeuchi, and H. Umezawa, *J. Antibiot.*, 1977, **30**, 1143; (c) M. Ceroni and U. Séquin, *Helv. Chim. Acta*, 1982, **65**, 302.
2. U. Séquin, in 'Progress in The Chemistry Of Organic Natural Products', ed. by W. Herz, H. Grisebach, G. W. Kirby, and C. Tamm, Springer, New York, 1986, p 57
3. Kidamycin: (a) N. Kanda, *J. Antibiot.*, 1971, **24**, 599; (b) N. Kanda, M. Kono, and K. Asano, *J. Antibiot.*, 1972, **25**, 553; (c) N. Kanda, *J. Antibiot.*, 1972, **25**, 599; (d) M. Furukawa, A. Itai, and Y. Iitaka, *Tetrahedron Lett.*, 1973, **14**, 1065; (e) M. Furukawa and Y. Iitaka, *Tetrahedron Lett.*, 1974, **15**, 3287; (f) M. Furukawa, I. Hayakawa, G. Ohta, and Y. Iitaka, *Tetrahedron*, 1975, **31**, 2989.
4. Hedamycin: (a) U. Séquin, C. T. Bedford, S. K. Chung, and A. I. Scott, *Helv. Chim. Acta*, 1977, **60**, 896; (b) U. Séquin, *Tetrahedron*, 1978, **34**, 761; (c) U. Séquin and M. Furukawa, *Tetrahedron*, 1978, **34**, 3623; (d) M. Zehnder, U. Séquin, and H. Nadig, *Helv. Chim. Acta*, 1979, **62**, 2525.
5. Saptomycins: (a) N. Abe, N. Enoki, Y. Nakakita, H. Uchida, R. Saito, and N. Watanabe, *J. Antibiot.*, 1991, **44**, 908; (b) N. Abe, N. Enoki, Y. Nakakita, H. Uchida, T. Nakamura, and M. Munekata, *J. Antibiot.*, 1993, **46**, 692; (c) N. Abe, Y. Nakakita, T. Nakamura, N. Enoki, H. Uchida, and M. Munekata, *J. Antibiot.*, 1993, **46**, 1530; (d) N. Abe, N. Enoki, Y. Nakakita, H. Uchida, T. Nakamura, and M. Munekata, *J. Antibiot.*, 1993, **46**, 1536.
6. M. R. Hansen and L. H. Hurley, *Acc. Chem. Res.*, 1996, **29**, 249.
7. For related natural products possessing an *N,N*-dimethylvancosamine *C*-glycoside, see, Rubiflavin A: H. Nadig and U. Séquin, *Helv. Chim. Acta*, 1980, **63**, 2446; (b) PD121, 222: H. Nadig, U. Séquin, R. H. Bunge, T. R. Hurley, D. B. Murphey, and J. C. French, *Helv. Chim. Acta*, 1985, **68**, 953; (c) epoxykidamycin: K. M. Byrne, S. K. Gonda, and B. D. Hilton, *J. Antibiot.*, 1985, **38**, 1040; (d) chromoxymycin: Y. Kawai, K. Furihata, H. Seto, and N. Otake, *Tetrahedron Lett.*, 1985, **26**, 3273; (e) rubiflavins: H. Nadig and U. Séquin, *Helv. Chim. Acta*, 1987, **70**, 1217; (f) ankinomycin: Y. Sato, H. Watabe, T. Nakazawa, T. Shomura, H. Yamamoto, M. Sezaki, and S. Kondo, *J. Antibiot.*, 1989, **42**, 149; (g) altromycins: G. M. Brill, J. B. McAlpine, D. N. Whittern, and A. M. Buko, *J. Antibiot.*, 1990, **43**, 229.
8. A. Fredenhagen and U. Séquin, *J. Antibiot.*, 1985, **38**, 236.
9. For examples of synthetic approaches to natural products with thermodynamically disfavored structure: see, reserpine: (a) R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey, and R. W. Kierstead, *Tetrahedron*, 1958, **2**, 1; (b) G. Stork, P. C. Tang, M. Casey, B. Goodman, and M. Toyota, *J. Am. Chem. Soc.*, 2005, **127**, 16255; cossinerine: (c) W. A. Ayer and K. Furuichi, *Can. J. Chem.*,

- 1976, **54**, 1494; (d) R. V. Stevens and A. W. M. Lee, *J. Am. Chem. Soc.*, 1979, **101**, 7032.
10. K. Kitamura, Y. Ando, T. Matsumoto, and K. Suzuki, *Chem. Rev.*, 2018, **118**, 1495.
  11. Y. Ando, K. Kitamura, T. Matsumoto, and K. Suzuki, Synthetic Approaches on the Pluramycin-Class Antibiotics. In *Cutting-Edge Organic Synthesis and Chemical Biology of Bioactive Molecules*; Y. Kobayashi, ed.; Springer: Singapore, 2019, pp. 75–100.
  12. K. Kitamura, Y. Ando, Y. Maezawa, T. Matsumoto, and K. Suzuki, *Heterocycles*, 2015, **90**, 1240.
  13. isokidamycin: (a) B. M. O’Keefe, D. M. Mans, D. E. Kaelin Jr., and S. F. Martin, *J. Am. Chem. Soc.*, 2010, **132**, 15528; (b) B. M. O’Keefe, D. M. Mans, D. E. Kaelin Jr., and S. F. Martin, *Tetrahedron*, 2011, **67**, 6524.
  14. saptomycin B: (a) K. Kitamura, Y. Ando, T. Matsumoto, and K. Suzuki, *Angew. Chem. Int. Ed.*, 2014, **53**, 1258; (b) K. Kitamura, Y. Maezawa, Y. Ando, T. Kusumi, T. Matsumoto, and K. Suzuki, *Angew. Chem. Int. Ed.*, 2014, **53**, 1262.
  15. M. D. Lewis, J. K. Cha, and Y. Kishi, *J. Am. Chem. Soc.*, 1982, **104**, 4976.
  16. (a) T. Matsumoto, M. Katsuki, H. Jona, and K. Suzuki, *Tetrahedron Lett.*, 1989, **30**, 6185; (b) T. Matsumoto, M. Katsuki, H. Jona, and K. Suzuki, *J. Am. Chem. Soc.*, 1991, **113**, 6982.
  17. T. Hosoya, Y. Ohashi, T. Matsumoto, and K. Suzuki, *Tetrahedron Lett.*, 1996, **37**, 663.
  18. J. Hartung, B. J. D. Wright, and S. J. Danishefsky, *Chem. Eur. J.*, 2014, **20**, 8731.
  19. For aryl  $\alpha$ -C-glucoside derivatives, (a) S. Xue, K.-Z. Han, L. He, and Q.-X. Guo, *Synlett*, 2003, 870; (b) S. Wagschal, J. Guilbaud, P. Rabet, V. Farina, and S. Lemaire, *J. Org. Chem.*, 2015, **80**, 9328.
  20. Z.-B. Fei and F. E. McDonald, *Org. Lett.*, 2007, **9**, 3547.
  21. K. Kitamura, M. Shigeta, Y. Maezawa, Y. Watanabe, D.-S. Hsu, Y. Ando, T. Matsumoto, and K. Suzuki, *J. Antibiot.*, 2013, **66**, 131.
  22. A. Ben, T. Yamauchi, T. Matsumoto, and K. Suzuki, *Synlett*, 2004, 225.
  23. E. L. Eliel, S. H. Wilen, and L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, 1994.
  24. These *O*-glycosides were isolated and fully characterized by spectroscopic means, see Supporting Information.
  25. These results were not fully optimized, so that the yields and ratio of the products have variation.
  26. The minor  $\beta$ -isomer adopted a normal chair conformation.