Efficient Bis-C-Aminoglycosylation toward the Synthesis of the Pluramycins

Masayuki Shigeta,[a,b] Tomohiko Hakamata,[a,b] Yukie Watanabe,[a,b] Kei Kitamura,[a,b] Yoshio Ando,[a,b] Keisuke Suzuki,*[a,b] Takashi Matsumoto*[b,c]

[a] Department of Chemistry, Tokyo Institute of Technology, O-okayama, Meguro, Tokyo, 152-8551, Japan

[b] Japan Science and Technology Agency (JST), SORST, O-okayama, Meguro, Tokyo, 152-8551, Japan

[c] School of Pharmacy, Tokyo University of Pharmacy and Life Sciences, Horinouchi, Hachioji, Tokyo, 192-0392, Japan
Fax +81(42)6763257; E-mail: tmatsumo@toyaku.ac.jp

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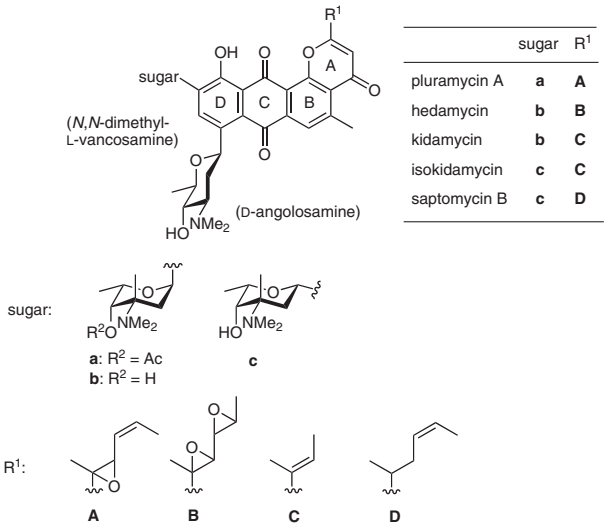
Abstract: Two bis-*C*-aminoglycosyl arenes containing the angolosamine and the vancosamine moieties, which are potentially useful as the D-ring fragments of the pluramycin-type antibiotics, were efficiently synthesized by the *O*→*C*-glycoside rearrangement based strategy.

Key words: natural product synthesis, pluramycin-type antibiotics, amino sugar, bis-*C*-glycoside, *O*→*C*-glycoside rearrangement

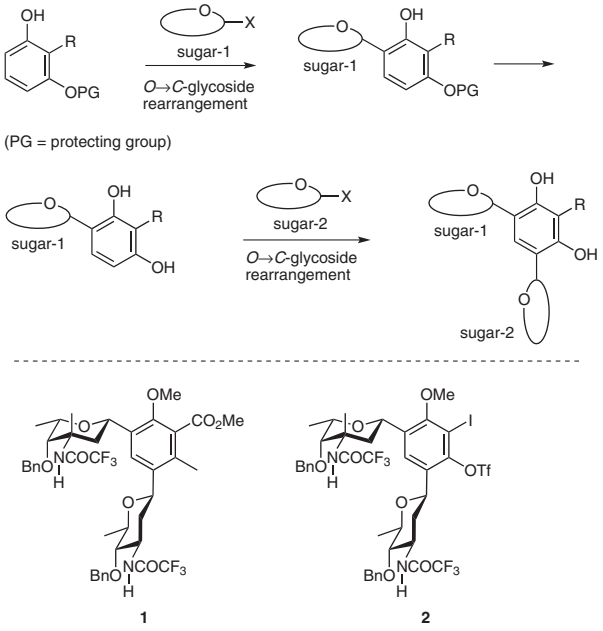
The pluramycins are a family of antibiotics featured by 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione chromophore with two amino sugars attached through the *C*-glycosidic linkages (Figure 1).[1] These compounds exhibit potent antitumor activity by DNA alkylation, where the two proximal amino sugars, D-angolosamine and *N*,*N*-dimethyl-L-vancosamine, play a key role in sequence recognition in intercalation of the tetracyclic chromophore.[2] Although such biochemical significance as well as the unique structure has made them attractive synthetic targets, no total synthesis has been recorded thus far.[3]



	sugar	R^1
pluramycin A	**a**	**A**
hedamycin	**b**	**B**
kidamycin	**b**	**C**
isokidamycin	**c**	**C**
saptomycin B	**c**	**D**

Figure 1

In our efforts toward the synthesis of these natural products, we previously reported an effective method for constructing bis-*C*-glycosyl arene structure by performing the *O*→*C*-glycoside rearrangement twice on a resorcinol derivative (Scheme 1).[4] Thus, the next questions to be addressed were, (1) whether the method would be adapted to the amino sugar system, and (2) whether the two phenolic hydroxy groups in the resulting bis-*C*-glycosyl arene could be managed to discriminate for the following transformations. Herein, we report that experimentation answered in the affirmative to these questions, thereby allowing the synthesis of bis-*C*-aminoglycosides **1** and **2**. They represent the first case of bis-*C*-glycosyl arenes furnished with both the angolosamine and the vancosamine moieties. Furthermore armed with the clues to the construction of the polycyclic skeleton, compounds **1** and **2** will serve as the useful D-ring fragments for the pluramycin synthesis.



Scheme 1

The synthesis of bis-*C*-glycoside **1** commenced with the C-glycosylation of monoprotected resorcylic ester **3**.[5] An extensive survey of the reaction conditions by employing glycosyl acetates **4**[6] and **6**[7] as the vancosamine and the angolosamine donors, respectively, proved that the reaction with **4** cleanly proceeded with $Sc(OTf)_3$ (20 mol%) and Drierite in dichloroethane[4] to afford β-*C*-glycoside **5** as the sole product in 88% yield (Scheme 2).[8] Predominant

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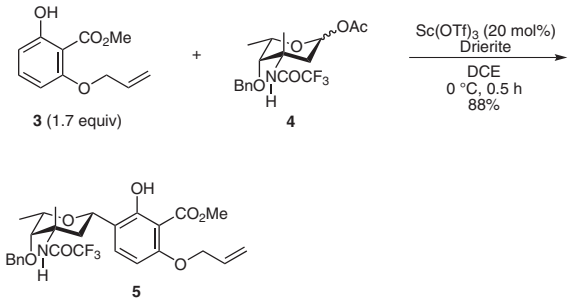
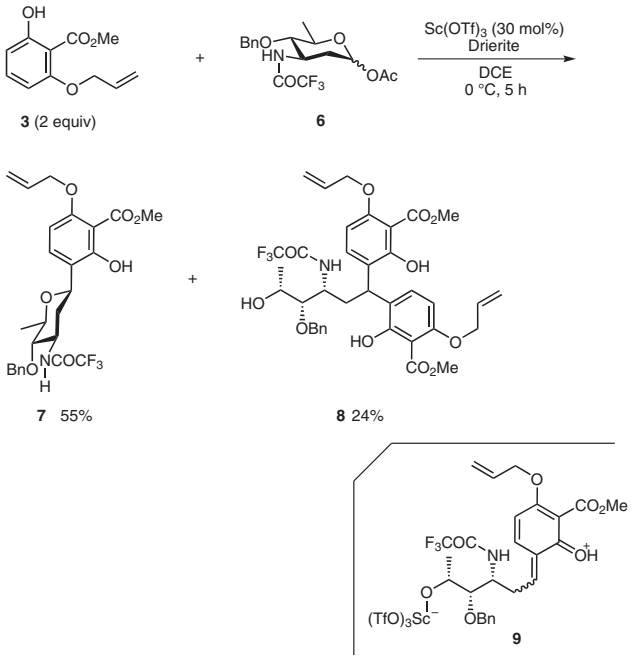
formation of the β-isomer is ascribable to the thermodynamic preference, since the possible α-isomer would suffer from significant steric repulsion between the C(6) methyl and the C(3) amide given the $^4C_1$ conformation dictated by the strong tendency of the C(1) aryl moiety to occupy the equatorial position.[9]



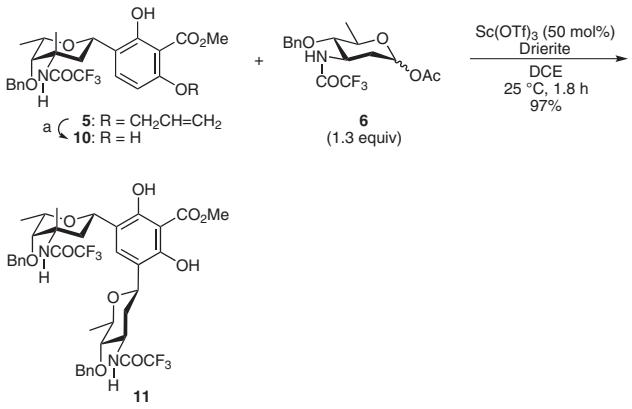
Scheme 2

The reaction of **3** with angolosaminyl acetate **6** also led to the desired β-*C*-glycoside **7** in good yield under the similar conditions, but along with many by-products (Scheme 3). Among such by-products, the major one was identified as the two-fold arylation product **8** (24%), presumably arising from Lewis acid promoted ring opening of **7** to generate the quinone methide like intermediate **9** followed by further attack of **3**.[10]

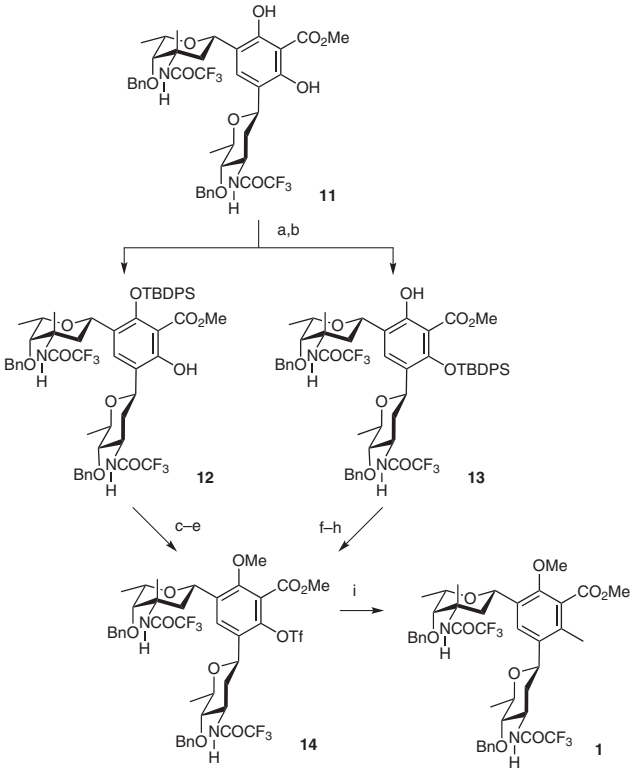


Scheme 3

Fortunately, however, angolosaminyl acetate **6** worked nicely in the installation of the second sugar moiety (Scheme 4). After removal of the allyl group from mono-*C*-glycoside **5**,[11] the resulting diol **10** was smoothly *C*-glycosylated with angolosaminyl acetate **6** (1.3 equiv) under the conditions involving $Sc(OTf)_3$ and Drierite to afford bis-*C*-glycoside **11** in 97% yield with no trace of the two-fold arylation. This result implied that the susceptibility of the angolosamine moiety to the two-fold arylation was reduced in **11** by the co-existing *C*-glycoside moiety [see the reaction of **3** with **6** (Scheme 3), where the angolosamine moiety in the mono-*C*-glycoside **7** suffered the two-fold arylation].[12]



Scheme 4 *Reagents and conditions*: (a) $Pd(OAc)_2$ (10 mol%), Ph_3P (40 mol%), HCO_2H, Et_3N, 1,4-dioxane, 60 °C, 15 min, 96%.

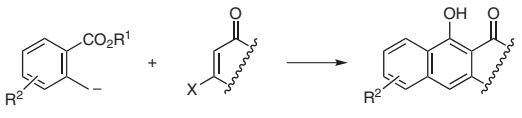


Scheme 5 *Reagents and conditions*: (a) NaH, (*t*-Bu)Ph_2SiCl, DMF, 0 °C, 93%; (b) Bu_4NF, MS 4A, THF, –30 °C, 89% (**12**:**13** = 3.2:1); (c) $PhNTf_2$, K_2CO_3, acetone, 25 °C, quant; (d) Bu_4NF, THF, 0 °C, 98%; (e) $(MeO)_2SO_2$, K_2CO_3, acetone, 25 °C, 92%; (f) $(MeO)_2SO_2$, K_2CO_3, acetone, 25 °C; (g) Bu_4NF, THF, 0 °C, 73% (2 steps); (h) $PhNTf_2$, K_2CO_3, acetone, 25 °C, 92%; (i) $(MeBO)_3$ (120 mol%), $Pd(PPh_3)_4$ (16 mol%), Cs_2CO_3 (3.4 equiv), 1,4-dioxane, 100 °C, 89%.

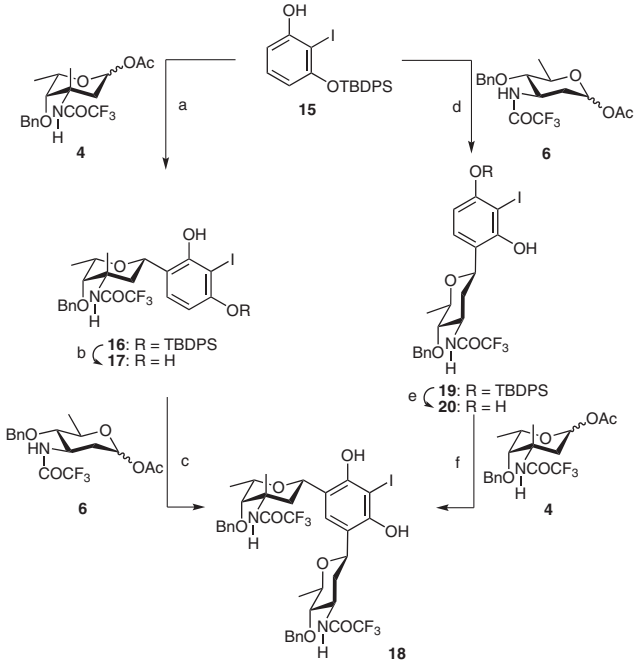
Conversion of bis-*C*-glycoside **11** into the target intermediate **1** was fairly effective, even if not very straightforward (Scheme 5). Since it was apparent that the two hydroxy groups in **11** were similar in their reactivity, we once protected both with *tert*-butyldiphenylsilyl groups, and examined monodesilylation of the resulting bissilyl ether. Fortunately, use of Bu_4NF under the controlled con-

ditions afforded a mixture of the monosilyl ethers, **12** and **13**, in high yield, which were easily separable by silica gel chromatography.[13] Each isomer converged into triflate **14** in high overall yield through the three-step sequence including triflation ($PhNTf_2$, K_2CO_3, acetone),[14] desilylation (Bu_4NF, THF), and methyl ether formation [$(MeO)_2SO_2$, K_2CO_3, acetone], in this order (for the isomer **12**) or the reverse order (for the isomer **13**). Finally, triflate **14**, upon reaction with trimethylboroxine under the Pd(0)-catalyzed conditions,[15] led to the desired bis-*C*-glycosylated *o*-toluate **1** in 89% yield.

Providing that the Staunton–Weinreb annulation[16] [i.e., the condensation of *o*-toluate-derived benzylic anion with Michael acceptors (Scheme 6)] tolerates the sugar moieties as the substituents, bis-*C*-glycoside **1** would be promising as the intermediate toward the construction of the polycyclic framework of the pluramycins.

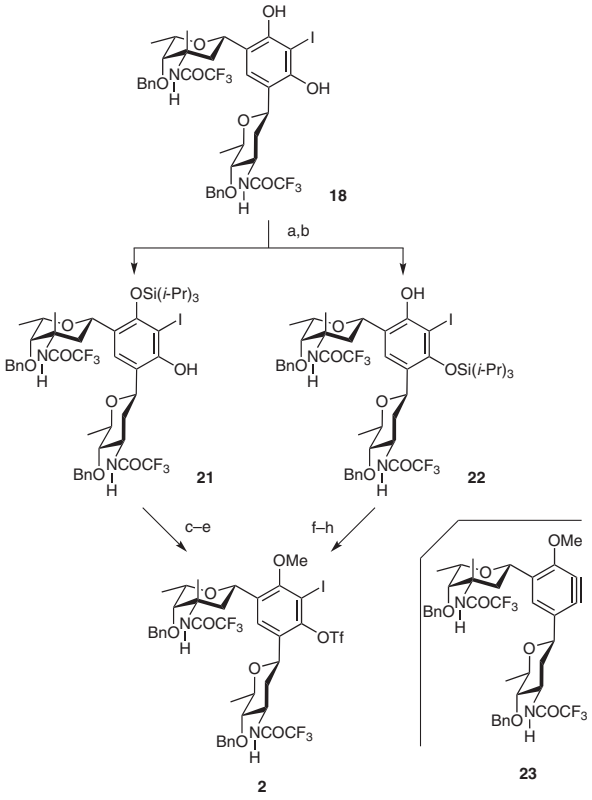


Scheme 6 The Staunton–Weinreb annulation



Scheme 7 *Reagents and conditions*: (a) **4** (1 equiv), **15** (1.9 equiv), $Sc(OTf)_3$ (30 mol%), Drierite, DCE, 0 °C, 8 h, 81%; (b) Bu_4NF, THF, 25 °C, 98%; (c) **6** (1.7 equiv), $Sc(OTf)_3$ (25 mol%), Drierite, DCE, 25 °C, 6 h, 77%; (d) **6** (1 equiv), **15** (2 equiv), $Sc(OTf)_3$ (25 mol%), Drierite, DCE, 0 °C, 5 h, 93%; (e) Bu_4NF, THF, 25 °C, 92%; (f) **4** (1.3 equiv), $Sc(OTf)_3$ (25 mol%), Drierite, DCE, 15 °C, 7 h, 80%.

ortho-Iodophenyl triflate **2**, the other target intermediate of ours, was synthesized in a similar way starting from monoprotected 2-iodoresorcinol **15**[17] (Scheme 7). In this synthesis, the order of the amino sugar installation did not make considerable difference to its efficiency. Both of the glycosyl donors worked nicely under the conditions employing $Sc(OTf)_3$ and Drierite in the first C-glycosylation of **15** and also in the second *C*-glycoside formation after desilylation.[18,19] Conversion of diol **18** to *o*-iodo triflate **2** was accomplished by utilizing again the bissilylation–monodesilylation sequence in high overall yield (Scheme 8).[13]



Scheme 8 *Reagents and conditions*: (a) NaH, $(i\text{-Pr})_3SiCl$, DMF, 0 °C, 92%; (b) Bu_4NF, MS 4A, THF, 0 °C, 87% (**21**:**22** = 1.7:1); (c) $PhNTf_2$, K_2CO_3, acetone, 25 °C, 99%; (d) Bu_4NF, THF, 0 °C, 89%; (e) $(MeO)_2SO_2$, K_2CO_3, acetone, 25 °C, 83%; (f) $(MeO)_2SO_2$, K_2CO_3, acetone, 25 °C, 97%; (g) Bu_4NF, THF, 0 °C, 86%; (h) $PhNTf_2$, K_2CO_3, acetone, 25 °C, 97%.

Compound **2**, thus obtained, could serve as the precursor of benzyne **23**, thereby allowing application to various cycloaddition reactions.[20]

In summary, the bis-*C*-glycoside synthesis based on the *O*→*C*-glycoside rearrangement was successfully applied to the amino sugar system to allow efficient access to the bis-*C*-aminoglycosides **1** and **2**, which contain the angolosamine and the vancosamine moieties and also the key clues to further elaboration of the aromatic ring. Further studies toward the total synthesis of the pluramycins are now underway in this laboratory.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

References and Notes

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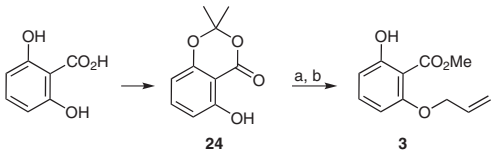
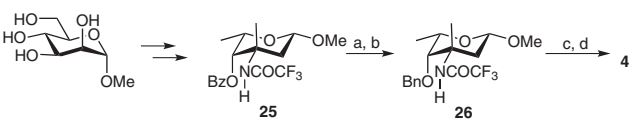
(5) Resorcylic ester **3** was synthesized as shown below (Scheme 9). For the preparation of the intermediate **24**, see: Hadfield, A.; Schweitzer, H.; Trova, M. P.; Green, K. *Synth. Commun.* **1994**, *24*, 1025.



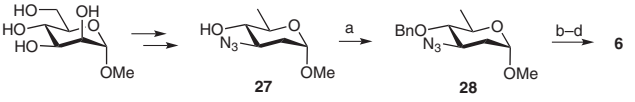
Scheme 9 *Reagents and conditions*: (a) CH_2=$CHCH_2Br$, K_2CO_3, acetone; (b) K_2CO_3, MeOH, 93% (2 steps).

(6) Vancosaminyl acetate **4** was synthesized as shown below (Scheme 10). (a) For the preparation of the intermediate **25**, see: Hsu, D.-S.; Matsumoto, T.; Suzuki, K. *Synlett* **2006**, 469. (b) For the selective alcoholysis of a benzoate by using $Mg(OMe)_2$, see: Xu, Y.-C.; Bizuneh, A.; Walker, C. *Tetrahedron Lett.* **1996**, *37*, 455.



Scheme 10 *Reagents and conditions*: (a) $Mg(OMe)_2$, MeOH, 25 °C, 70%; (b) NaH, BnBr, DMF, 0 °C, 83%; (c) 20% AcOH, 100 °C; (d) Ac_2O, 4-DMAP, pyridine, 92% (2 steps).

(7) Angolosaminyl acetate **6** was synthesized as shown below (Scheme 11). For the preparation of the intermediate **27**, see: Bartner, P.; Boxler, D. L.; Brambilla, R.; Mallams, A. K.; Morton, J. B.; Reichert, P.; Sancilio, F. D.; Surprenant, H.; Tomalesky, G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1600.



Scheme 11 *Reagents and conditions*: (a) NaH, BnBr, DMF, 92%; (b) Ph_3P, CH_2Cl_2 then $(CF_3CO)_2O$, Et_3N, 83%; (c) 20% AcOH, 100 °C; (d) Ac_2O, 4-DMAP, pyridine, 83% (2 steps).

(8) The anomeric configurations in **5** and **11** (Figure 2) were determined by the coupling constants of ^1H NMR spectra and NOE measurements. For details, see Supporting Information.

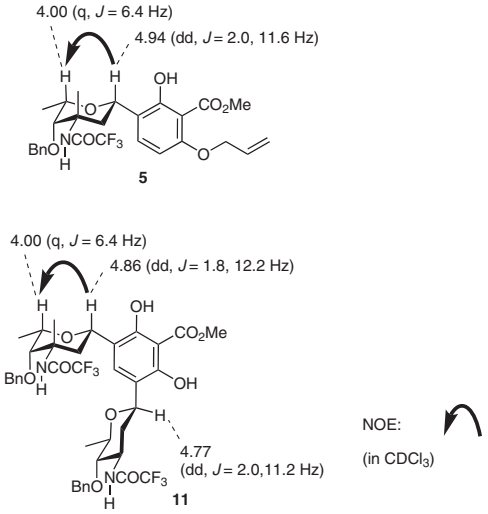
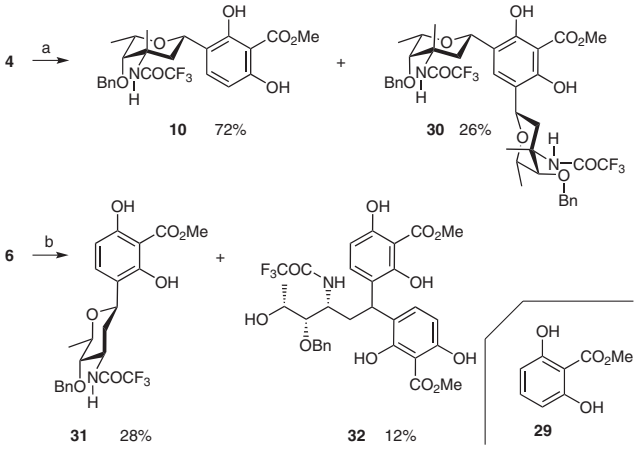


Figure 2

(9) (a) Hosoya, T.; Ohashi, Y.; Matsumoto, T.; Suzuki, K. *Tetrahedron Lett.* **1996**, *37*, 663. (b) Also see reference 4e.

(10) It is interesting to note that vancosaminyl acetate **4** upon reaction with excess resorcylic ester **29** (3 molar amounts) gave mono-*C*-glycoside **10** and bis-*C*-glycoside **30** in high combined yield without formation of the two-fold arylation product (Scheme 12). In contrast, the reaction of angolosaminyl acetate **6** with **29** (2 molar amounts) gave none of the bis-*C*-glycoside but yielded mono-*C*-glycoside **31** (28% yield), the two-fold arylation product **32** (12%), and many other unidentified products of higher molecular weights. It is therefore obvious that the angolosamine moiety is much more apt to undergo the two-fold arylation, as compared with the vancosamine moiety. We surmise the steric congestion at the C(3) position in the vancosamine moiety makes it resistant to this unfavorable reaction.



Scheme 12 *Reagents and conditions*: (a) **29** (3 equiv), $Sc(OTf)_3$ (25 mol%), Drierite, DCE, 5 °C, 2 h; (b) **29** (2 equiv), $Sc(OTf)_3$ (25 mol%), Drierite, DCE, 0 °C, 23 h.

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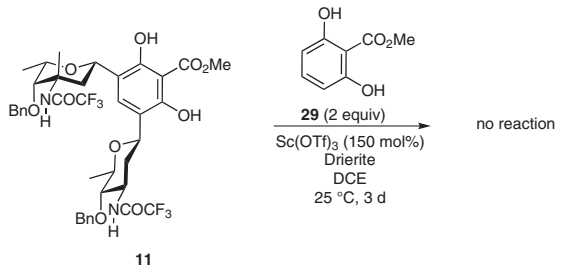
(12) Actually, treatment of bis-*C*-glycoside **11** with excess amounts of diol **29** under the $Sc(OTf)_3$–Drierite conditions led to the complete recovery of **11** (Scheme 13).



Scheme 13

(13) For determination of the regiochemistry, see Supporting Information.

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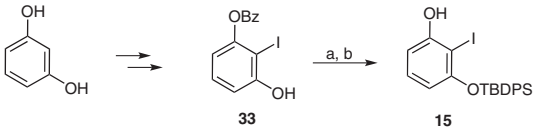
(17) Iodoresorcinol **15** was synthesized as shown below (Scheme 14). For the preparation of the intermediate **33**, see: (a) Hamura, T.; Hosoya, T.; Yamaguchi, H.; Kuriyama, Y.; Tanabe, M.; Miyamoto, M.; Yasui, Y.; Matsumoto, T.; Suzuki, K. *Helv. Chim. Acta* **2002**, *85*, 3589. (b) Tsujiyama, S.; Suzuki, K. *Org. Synth.* **2007**, *84*, 272.



Scheme 14 *Reagents and conditions*: (a) (*t*-Bu)Ph_2SiCl, imidazole, DMF, 93%; (b) $Me_2N(CH_2)_3NH_2$, Et_3N, THF, 95%.

(18) The anomeric configurations in **16** and **18** (Figure 3) were determined by the coupling constants of ^1H NMR and NOE measurements. For details, see Supporting Information.

(19) So far, we have never encountered the two-fold arylation in the C-glycosylation of various 2-iodoresorcinol derivatives, regardless of the glycosyl donors (see references 4, 20b–d). Furthermore, it turned out that mono-*C*-glycosides **19** and **20** possessing the angolosamine moieties were recovered intact even after treatment with two molar amounts of diol **29** under the conditions with excess $Sc(OTf)_3$ (Scheme 15). These results, setting the reason aside, imply that susceptibility of the *C*-glycoside moiety to the two-fold arylation depends on the C(2)-substituent of the resorcinol moiety, in addition to the structure of the sugar moiety as described in reference 10.

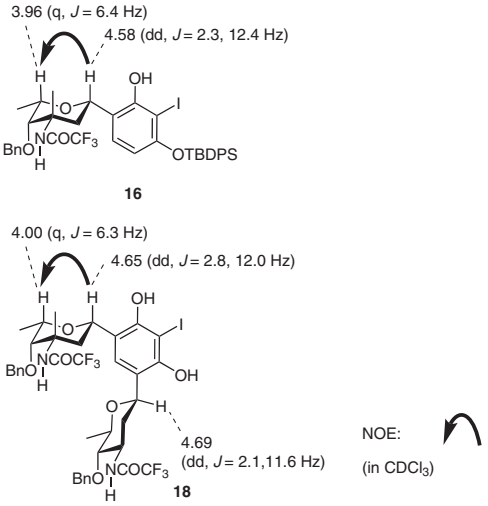
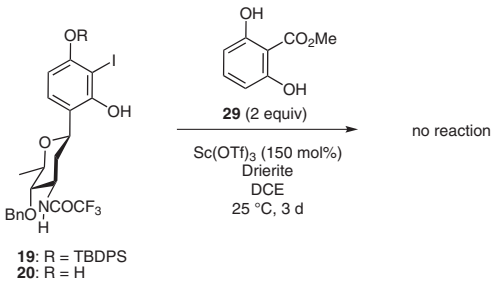


Figure 3



Scheme 15

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