

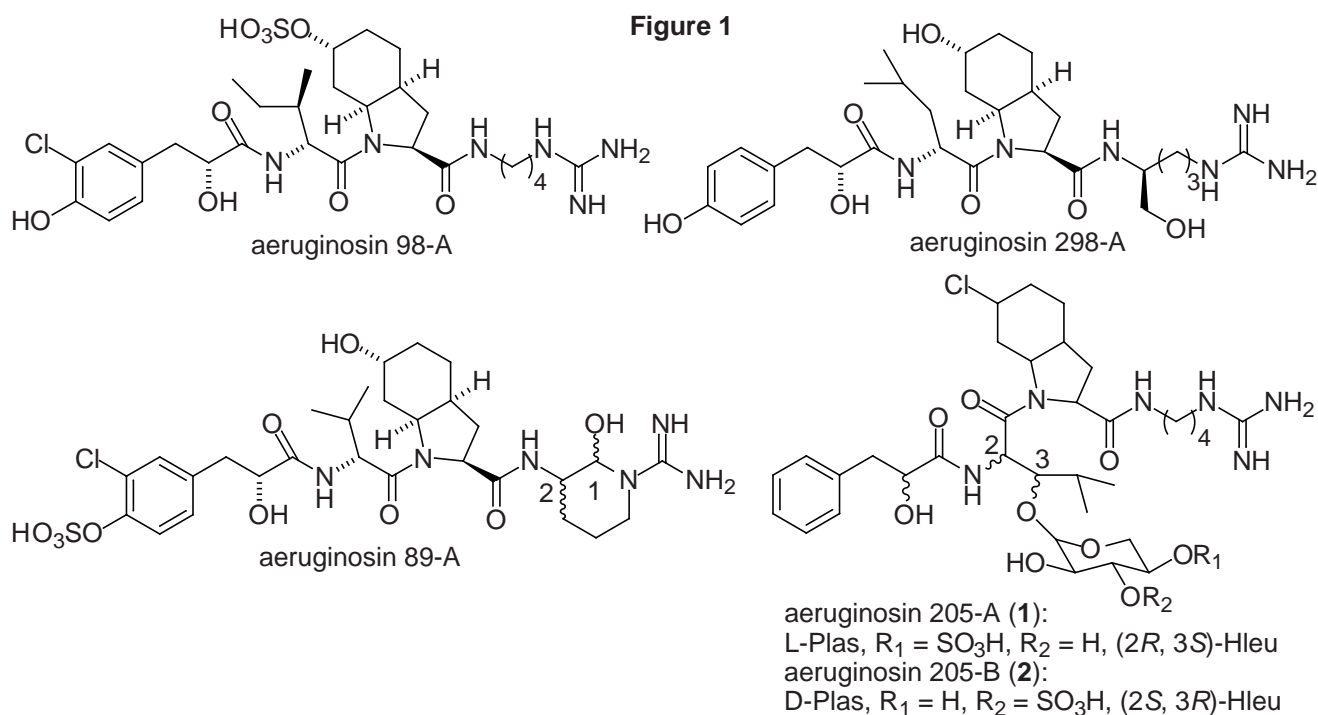
## SYNTHESIS OF THE *N*-TERMINUS OF GLYCOPEPTIDE UNIT FOR AERUGINOSIN 205-A

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**Abstract** - The *N*-terminus moiety of glycopeptide unit for aeruginosin 205-A has been synthesized.

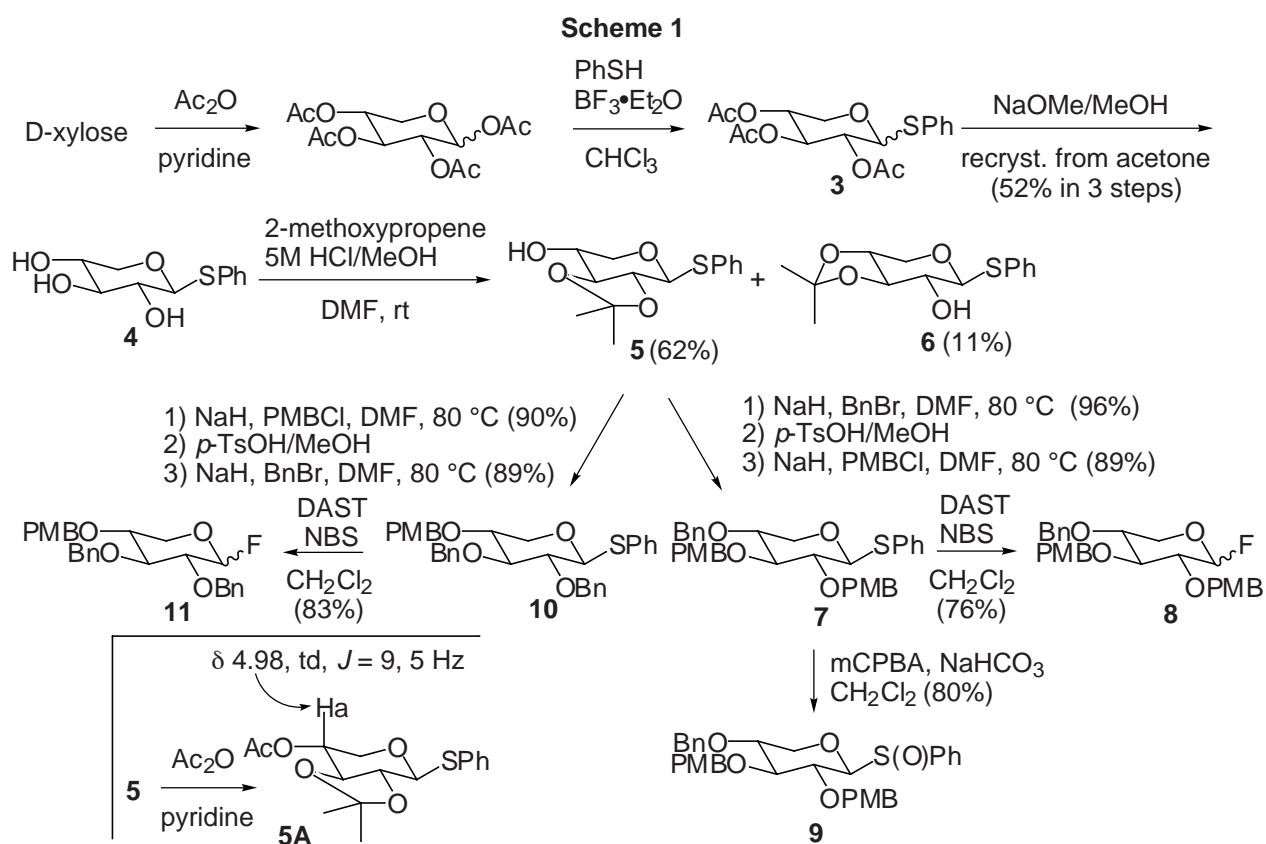
Aeruginosins, isolated from the cyanobacteria by Murakami,<sup>1</sup> showed significant inhibitory activity against trypsin and thrombin.<sup>2</sup> Many of aeruginosins have a 2-carboxy-6-hydroxyoctahydroindole (Choi) core unit, an arginine derivative as the *C*-terminus, an amide of *p*-hydroxyphenyllactic acid derivative and a normal amino acid as the *N*-terminus. Out of aeruginosins, 205-A (**1**)<sup>3</sup> and 205-B (**2**)<sup>3</sup> have a 2-carboxy-6-chlorooctahydroindole (Ccoi) core unit<sup>4</sup> instead of Choi and an unique glycopeptide bearing an  $\alpha$ -glycoside as the *N*-terminus of Ccoi.



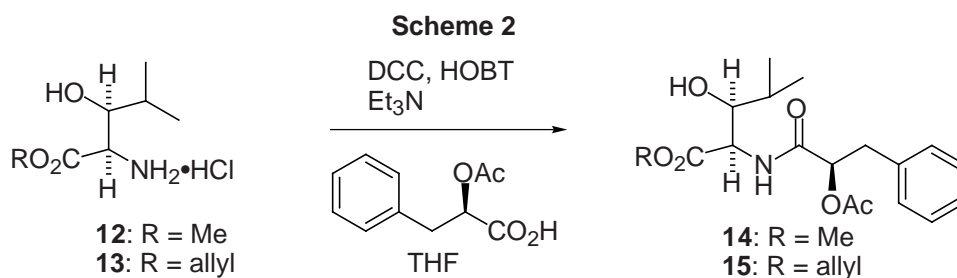
Both aeruginosins 205-A and B inhibited trypsin with an IC<sub>50</sub> of 0.07  $\mu$ g/mL, and inhibited thrombin with IC<sub>50</sub> values of 1.5  $\mu$ g/mL for **1** and 0.17  $\mu$ g/mL for **2**. The unique structural feature and intriguing

biological activity of aeruginosins have attracted the increasing attention of organic chemists and quite recently, total synthesis and stereochemical revision of aeruginosin 298-A were reported.<sup>5</sup> We now report the synthesis of glycopeptide unit for **1**.

Acetylation of D-xylose gave tetraacetate, which was transformed into phenylthio derivative (**3**). Hydrolysis of **3** with NaOMe gave triol, which was recrystallized from acetone to afford pure triol (**4**), mp 137~138 °C, in 52% yield over 3 steps. Treatment of **4** with 2-methoxypropene in the presence of catalytic amounts of 5M HCl/MeOH in DMF at room temperature afforded acetonides (**5**)<sup>6</sup> and (**6**) in 62% and 11% yields, respectively. The acetonide (**5**) was converted to several glycosyl donors for glycosylation reaction as shown in Scheme 1.

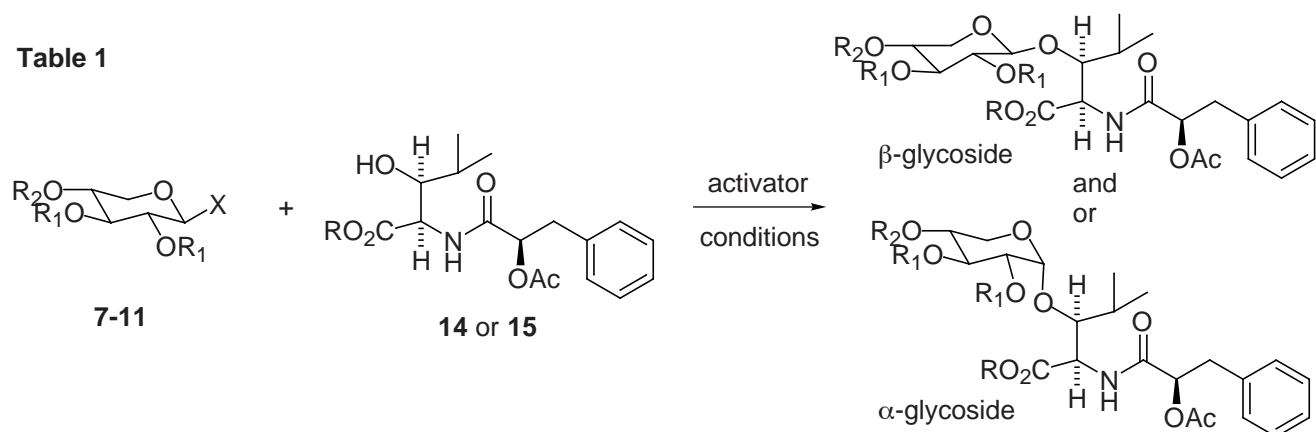


On the other hand, the glycosyl acceptors of the amide alcohols (**14**, **15**) were prepared (40% for **14** and 32% for **15**) from methyl (**12**)<sup>7</sup> or allyl (**13**)<sup>7</sup> (2*R*, 3*S*)-3-hydroxyleucinate and acetyl phenyllactic acid under the standard procedure as shown in Scheme 2.



With the requisite glycosyl donors (**7-11**) and acceptors (**14**, **15**) in hand, we next focused our attention on the glycosylation reaction. The result was summarized in Table 1. Interestingly, the use of the *p*-methoxybenzyl protective group on the C<sub>2</sub>-hydroxyl of the glycosyl donors gave β-glycosides exclusively (Runs 1~4). The use of benzyl protective group on the C<sub>2</sub>-hydroxyl afforded a mixture of α- and β-glycosides (Runs 5, 7).

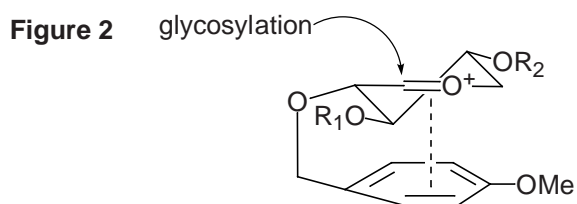
**Table 1**



Run	Glycosyl donor	Glycosyl acceptor	Activator	Conditions	Ratio (α : β) <sup>a</sup>	Yield (%) <sup>b</sup>
1	R <sub>1</sub> = PMB, R <sub>2</sub> = Bn, X = SPh ( <b>7</b> )	R = Me ( <b>14</b> )	MeOTf <sup>8</sup>	MS4A, Et <sub>2</sub> O, 0 °C~rt	0 : 1	63
2	R <sub>1</sub> = PMB, R <sub>2</sub> = Bn, X = SPh ( <b>7</b> )	R = Me ( <b>14</b> )	NIS, TfOH <sup>9</sup>	MS4A, dichloroethane, 0 °C	0 : 1	58
3	R <sub>1</sub> = PMB, R <sub>2</sub> = Bn, X = F ( <b>8</b> )	R = Me ( <b>14</b> )	SnCl <sub>2</sub> , AgClO <sub>4</sub> <sup>10</sup>	MS4A, Et <sub>2</sub> O, -20 °C~rt	0 : 1	75
4	R <sub>1</sub> = PMB, R <sub>2</sub> = Bn, X = S(O)Ph ( <b>9</b> )	R = Me ( <b>14</b> )	Tf <sub>2</sub> O <sup>11</sup>	MS4A, toluene, -78 °C~-60 °C	0 : 1	66
5	R <sub>1</sub> = Bn, R <sub>2</sub> = PMB, X = SPh ( <b>10</b> )	R = allyl ( <b>15</b> )	MeOTf <sup>8</sup>	MS4A, Et <sub>2</sub> O, 0 °~rt	1 : 1	66
6	R <sub>1</sub> = Bn, R <sub>2</sub> = PMB, X = SPh ( <b>10</b> )	R = allyl ( <b>15</b> )	NIS, TfOH <sup>9</sup>	MS4A, dichloroethane, 0 °C	0 : 1	40
7	R <sub>1</sub> = Bn, R <sub>2</sub> = PMB, X = F ( <b>11</b> )	R = allyl ( <b>15</b> )	SnCl <sub>2</sub> , AgClO <sub>4</sub> <sup>10</sup>	MS4A, Et <sub>2</sub> O, -20 °C~rt	1 : 2	72
8	R <sub>1</sub> = Bn, R <sub>2</sub> = PMB, X = F ( <b>11</b> )	R = allyl ( <b>15</b> )	Cp <sub>2</sub> ZrCl <sub>2</sub> , AgClO <sub>4</sub> <sup>12</sup>	MS4A, toluene, -78 °C~rt	no reaction	

a: The ratio of α- and β-glycosides was isolated one. The structure of α- and β-glycosides was determined by the <sup>1</sup>H-NMR (δ 4.84, d, *J* = 1.7 Hz for α-glycoside, δ 4.34, d, *J* = 7.3 Hz for β-glycoside) and <sup>13</sup>C-NMR (δ 97.29 for α-glycoside, δ 102.01 for β-glycoside) spectra of both glycosides. b: Yields were combined ones, respectively.

It seems that the electron-rich *p*-methoxyphenyl ring in the PMB ether on the C<sub>2</sub>-hydroxyl affects the β-selectivity in the above glycosylation reaction as shown in Figure 2.



Although, the above explanation is still speculative, it is the first example that the *p*-methoxybenzyl group effects as a neighboring group for selective glycosylation.

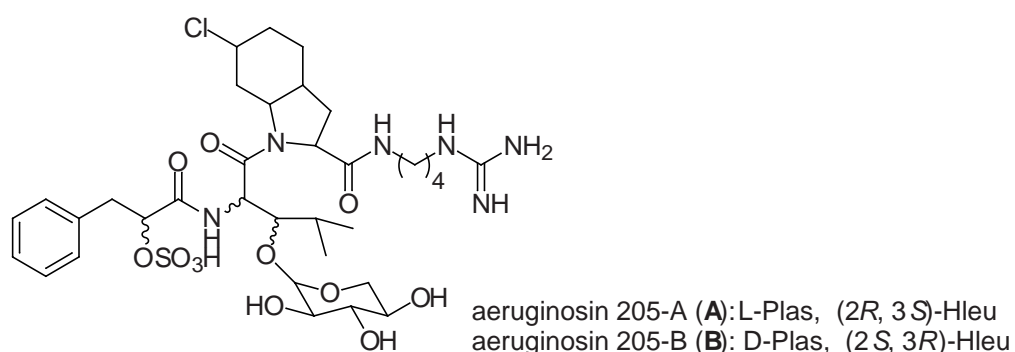
In conclusion, we achieved the synthesis of glycopeptide bearing an  $\alpha$ -glycoside for aeruginosin 205-A (**1**). Synthesis of Ccoi unit and coupling the reaction of glycopeptide with Ccoi is now being examined.

## ACKNOWLEDGMENT

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