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

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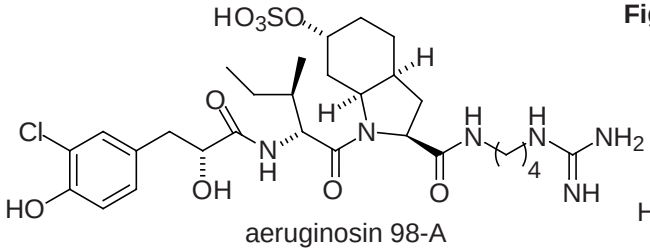
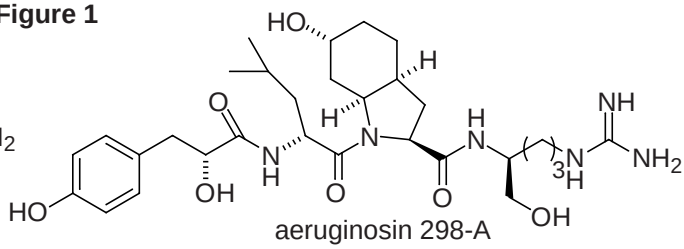
Abstract - The *N*-terminus moiety of glycopeptide unit for aeruginosin 205-A has been synthesized.

Aeruginosins, isolated from the cyanobacteria by Murakami,[1] showed significant inhibitory activity against trypsin and thrombin.[2] 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**)[3] and 205-B (**2**)[3] have a 2-carboxy-6-chlorooctahydroindole (Ccoi) core unit[4] instead of Choi and an unique glycopeptide bearing an α-glycoside as the *N*-terminus of Ccoi.

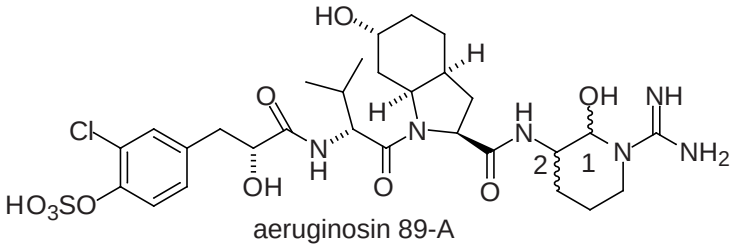
Figure 1



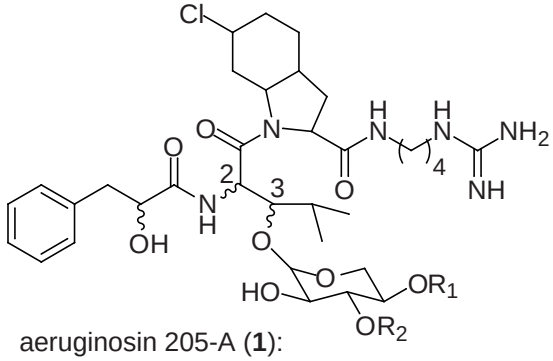
aeruginosin 98-A



aeruginosin 298-A



aeruginosin 89-A



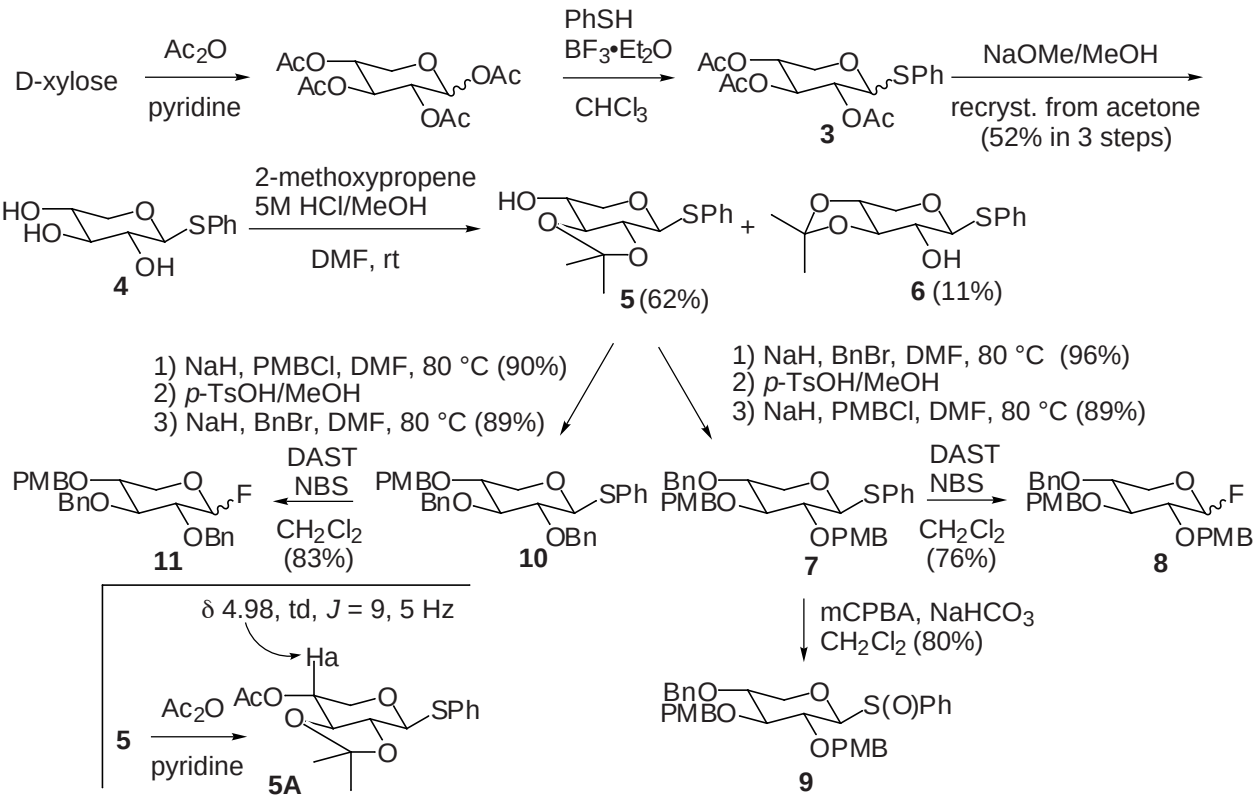
aeruginosin 205-A (**1**):
L-Plas, R_1 = SO_3H, R_2 = H, (2*R*, 3*S*)-Hleu
aeruginosin 205-B (**2**):
D-Plas, R_1 = H, R_2 = SO_3H, (2*S*, 3*R*)-Hleu

Both aeruginosins 205-A and B inhibited trypsin with an IC_{50} of 0.07 μg/mL, and inhibited thrombin with IC_{50} values of 1.5 μg/mL for **1** and 0.17 μg/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.[5] We now report the synthesis of glycopeptide unit for **1**.

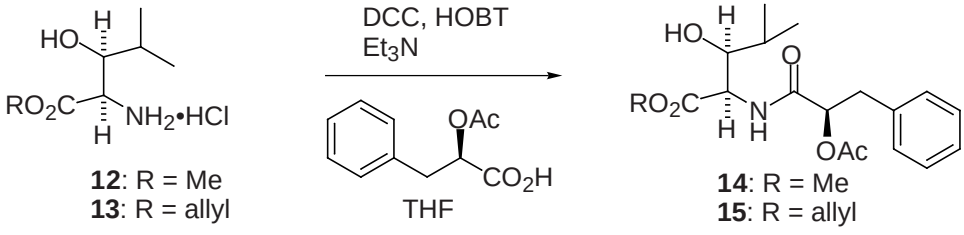
Acetylation of D-xylose gave tetraacetate, which was transformed into phenylthio derivative (**3**). Hydrolysis of **3** with NaOMe gave triol, which was recrystallized from acetone to afford pure triol (**4**), mp 137~138 ℃, in 52% yield over 3 steps. Treatment of **4** with 2-methoxypropene in the presense of catalytic amounts of 5M HCl/MeOH in DMF at room temperature afforded acetonides (**5**)[6] 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.

Scheme 1



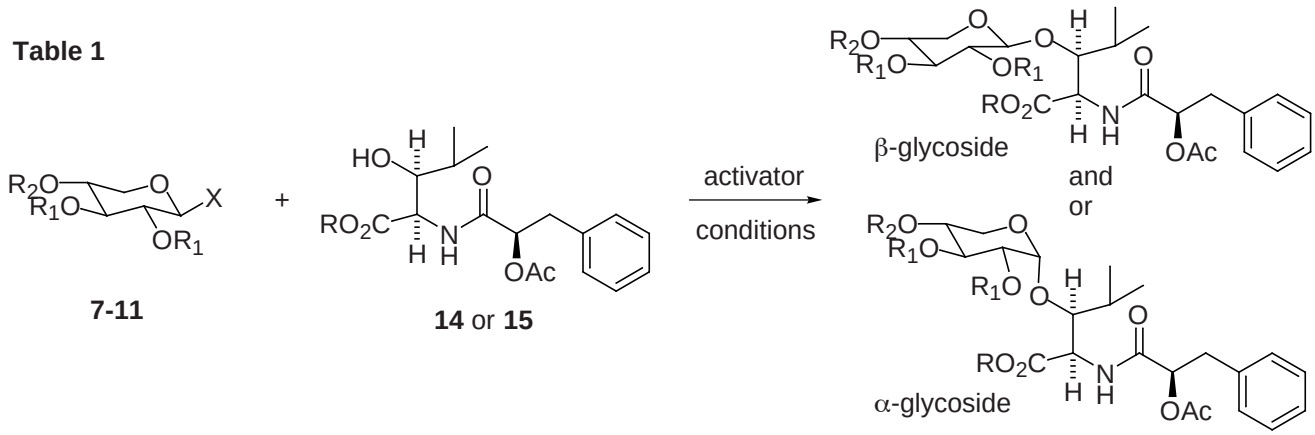
On the other hand, the glycosyl acceptors of the amide alcohols (**14**, **15**) were prepared (40% for **14** and 32% for **15**) from methyl (**12**)[7] or allyl (**13**)[7] (2*R*, 3*S*)-3-hydroxyleucinate and acetyl phenyllactic acid under the standard procedure as shown in Scheme 2.

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_2-hydroxyl of the glycosyl donors gave β-glycosides exclusively (Runs 1~4). The use of benzyl protective group on the C_2-hydroxyl afforded a mixture of α- and β-glycosides (Runs 5, 7).

Table 1



7-11

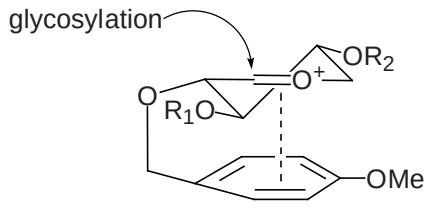
14 or **15**

Run	Glycosyl donor	Glycosyl aceptor	Activator	Conditions	Ratio (α : β)[a]	Yield (%)[b]
1	R_1 = PMB, R_2 = Bn, X = SPh (**7**)	R = Me (**14**)	MeOTf [8]	MS4A, Et_2O, 0 ℃~rt	0 : 1	63
2	R_1 = PMB, R_2 = Bn, X = SPh (**7**)	R = Me (**14**)	NIS, TfOH[9]	MS4A, dichloroethane, 0 ℃	0 : 1	58
3	R_1 = PMB, R_2 = Bn, X = F (**8**)	R = Me (**14**)	$SnCl_2$, $AgClO_4$ [10]	MS4A, Et_2O, –20 ℃~rt	0 : 1	75
4	R_1 = PMB, R_2 = Bn, X = S(O)Ph (**9**)	R = Me (**14**)	Tf_2O[11]	MS4A, toluene, –78 ℃~–60 ℃	0 : 1	66
5	R_1 = Bn, R_2 = PMB, X = SPh (**10**)	R = allyl (**15**)	MeOTf [8]	MS4A, Et_2O, 0 ℃~rt	1 : 1	66
6	R_1 = Bn, R_2 = PMB, X = SPh (**10**)	R = allyl (**15**)	NIS, TfOH[9]	MS4A, dichloroethane, 0 ℃	0 : 1	40
7	R_1 = Bn, R_2 = PMB, X =F (**11**)	R = allyl (**15**)	$SnCl_2$, $AgClO_4$ [10]	MS4A, Et_2O, –20 ℃~rt	1 : 2	72
8	R_1 = Bn, R_2 = PMB, X = F (**11**)	R = allyl (**15**)	Cp_2ZrCl_2, $AgClO_4$ [12]	MS4A, toluene –78 ℃~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 ^{1}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 ^{13}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_2-hydroxyl affects the β-selectivity in the above glycosylation reaction as shown in Figure 2.

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 α-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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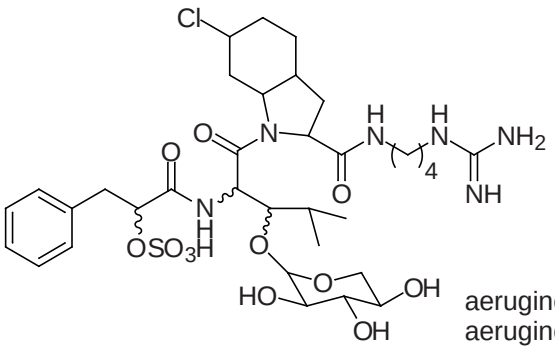
Later, the structure was revised to **1** for 205-A and **2** for 205-B; M. Murakami, personal communications.



aeruginosin 205-A (**A**): L-Plas, (2*R*, 3*S*)-Hleu
aeruginosin 205-B (**B**): D-Plas, (2*S*, 3*R*)-Hleu

4 Although, the absolute stereochemistry of Choi core unit for aeruginosins was determined by the comparison of the NMR spectra of (*R*)- and (*S*)-PGME amides derived from Choi diacetate by Murakami,[1e] and two total syntheses of aeruginosin 298-A,[5] the absolute stereochemistry of Ccoi has not been determined yet.

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