A number of natural glycosidase inhibitors and synthetic analogues were reported for potential therapeutic uses in diabetic mellitus,1 tumor metastases,2 and acquired immunodeficiency syndrome.3 Development of improved synthetic methodologies for glycosidase inhibitors is still a challenging field. Recently, two different innovated synthetic approaches toward pyrrolidine alkaloid derivatives were published.4 Various synthetic methodologies have been applied for preparing dideoxynojirimycin derivatives as drug candidates.5 In this communication, a new synthetic strategy toward dideoxynojirimycin derivatives is proposed. In order to minimize the sequential protection-deprotection steps for OH group in carbohydrate chemistry, we chose dehydroamino acid as a key intermediate which was prepared by condensation between amino acid derivative and tetrose building block. Finally intramolecular cyclization reaction of dehydroamino acid intermediate would construct the 6 membered ring structure of dideoxynojirimycin.

For the preparation of dehydroamino acid intermediate 5Z/E, modified Horner-Emmons reaction between ethylphosphono-glycinate 4 and tetrose building block 3 gave the best result.6 (Scheme 1) Ethyl-N-trifluoroacetyl-phosphono-glycinate 4 was prepared by free radical bromination of ethyl-N-trifluoroacetyl-glycinate with NBS followed by an Arbuzov reaction.7 Tetrose building block 3 was synthesized from L-threose diethylthioacetal (1) through tritylation of 4-OH and p-methoxybenzylations of 2 and 3-OH groups.8

The condensation between 3 and 4 with lithium diisopropylamide (LDA) gave a mixture of two isomers 5Z/E in a 3 : 1 ratio, and the major product was figured out as a Z isomer by chemical shift of vinyl proton in H NMR data. Trityl protection group of 5Z was removed by adding 75% acetic acid, and the resulting OH was converted into mesylate by the reaction with mesyl chloride in pyridine.

At the beginning, spontaneous intramolecular cyclization

\[
\begin{align*}
\text{Scheme 1}
\end{align*}
\]
toward 7 was expected after removal of N-trifluoroacetyl protection group of 6 by treating K₂CO₃ in aqueous methanol. However, a mixture of products was obtained, and the expected product 7 could not be separated. For a model study, 8 was synthesized, and deprotection of N-trifluoroacetyl group followed by intramolecular cyclization was performed by adding K₂CO₃ in aqueous methanol at 60 °C. The cyclized product 9 was isolated with 82% yield. However, the reaction of 10 in the same condition gave picolinic ester 11 as a major product. It is clear that unwanted elimination of p-methoxy benzyl (PMB) or isopropylidene groups occurred after the intramolecular cyclization, and finally more stable aromatic compound was produced.

The tendency of elimination of 6 might be much less than 10, because picolinic ester was not found in the product mixture. Therefore, less basic condition for the deprotection of trifluoroacetyl group was required to get the desired product 7. When 6 was treated with NaBH₄ in ethanol at room temperature, only cyclized product 7 was obtained in 42% yield. Compound 7 itself is an interesting dideoxynojirimycin derivative as well as an important intermediate for 4-amino-1,4-dideoxynojirimycin derivatives by introducing amino group by Michael addition. Synthesis and biological activities of 4-amino-1,4-dideoxynojirimycin derivatives have not been reported yet.

When 6 was treated with hydroxylamine hydrochloride and LDA in DMF solution, instead of a pyrrolidine derivative 13 or 14, only 12 was produced in 40% yield as a result of simple 5,2 reaction of hydroxylamine. (Scheme 2) It was an surprising result because another dehydroamino acid 15 was completely converted into a bicyclic 3-isoxazolidinone derivative 17 via piperidine derivative 16 under the same reaction condition. Probably, steric hindrance or ring strain of 13 might be too serious for compound 12 to perform intramolecular Michael addition. However, further studies are necessary to figure out the exact reason why 5-membered ring formation of 13 is less favorable than 6-membered ring formation of 16 or 17.

In conclusion, facile synthesis of a dehydroamino acid which has a sugar moiety at its side chain was performed, and new synthetic scheme using a dehydroamino acid as a key intermediate was proved to be an effective method for preparing dideoxynojirimycin derivatives. Further studies are under progress for functionalizing the double bond of dideoxynojirimycin 7 by reduction, oxidation, and Michael addition of various nucleophiles.

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References
10. ¹H NMR and ¹³C NMR of compound 7 were taken by Bruker AMX 500 MHz NMR, and spectral data are as follows. ¹H NMR of 7 (CDCl₃): 7.18 (t, J = 8.88, 8.88 Hz, 4H, ArH) 6.87 (m, 4H, ArH), 6.35 (d, J = 1.1, 3.7 Hz, 1H, vinyl-H), 4.46 (m, 4H, OCH₂Ar), 4.25 (d, J = 1.4, 7.1 Hz, 2H, OCH₂CH₃), 4.10 (d, J = 15 Hz, 1H, CH₂NH), 3.87 (m, 1H, CHOPMB), 3.71 (d, J = 2.48 Hz, 1H, ArOCH₂), 3.76 (m, 1H, CHOPMB). 3.41 (d, J = 13.4 Hz, 1H, CH₂NH), 1.37 (m, 3H, OCH₂CH₃). ¹³C NMR of 7: 162.2, 159.6, 159.5, 132.7, 129.5, 129.3, 123.7, 114.1, 114.0, 73.2, 71.3, 71.0, 70.6, 70.4, 61.9, 55.3, 45.4, 31.9, 29.7, 29.3, 22.7, 14.1, 13.9.
11. ¹H NMR and ¹³C NMR of compound 12 were taken by Bruker AMX 500 MHz NMR, and spectral data are as fol-
Following. $^1$H NMR of 12 (CDCl$_3$): 8.43 (s, 1H, CF$_3$CONH), 7.20 (m, 4H, ArH), 6.85 (m, 4H, ArH), 6.45 (d, $J = 7.2$ Hz, 1H, vinyl-H), 4.67 (d, $J = 11.1$ Hz, 1H, OCH$_2$Ar), 4.59 (m, 2H, OCH$_2$Ar), 4.30 (m, 4H, OCH$_2$Ar. OCH$_2$CH$_3$, CHOPMB), 3.80 (d, $J = 2.8$ Hz, 6H, ArOCH$_3$), 3.75 (m, 1H, CH$_2$NH). $^{13}$C NMR of 12: 162.3, 159.8, 159.6, 131.4, 130.2, 129.9, 128.7, 128.6, 128.2, 114.0, 113.9, 80.2, 74.2, 73.5, 71.7, 62.1, 55.2, 42.2, 31.9, 29.7, 29.3, 29.1, 22.7, 14.1, 14.0

12. $^1$H NMR and $^{13}$C NMR of compound 17 were taken by Bruker 360 MHz NMR, and spectral data are as following. $^1$H NMR of 17 (DMSO-d$_6$): 7.24 (m, 4H, ArH), 7.16 (m, 2H, ArH), 6.91 (m, 6H, ArH), 4.95 (dd, $J = 8.44$, 10.99 Hz, 1H, NCHCO), 4.62 (d, $J = 11.57$ Hz, 1H, OCH$_2$Ar), 4.51 (d, $J = 11.61$ Hz, 1H, OCH$_2$Ar), 4.51 (d, $J = 3.91$ Hz, 2H, OCH$_2$Ar), 4.43 (d, $J = 11.31$ Hz, 1H, OCH$_2$Ar), 4.39 (d, $J = 11.30$ Hz, 1H, OCH$_2$Ar), 3.95 (dd, $J = 3.08$, 3.08 Hz, 1H, CHOPMB), 3.86 (m, 1H, CHOPMB), 3.75 (m, 7H, ArOCH$_3$, ArOCH$_3$, CHNO), 3.74 (s, 3H, ArOCH$_3$), 3.70 (m, 1H, CHOPMB), 3.65 (dd, $J = 3.91$, 8.27 Hz, 1H, CH$_2$NO), 3.05 (brd, 1H, CH$_2$NO); $^{13}$C NMR of 17: 170.3, 159.7, 159.4, 159.1, 157.4 (dd, $J = 37.2$, 37.2, 37.2 Hz, CF$_3$CO), 133.0, 130.1, 129.9, 129.6, 129.5, 129.3, 129.2, 129.0, 128.6, 115.3 (dd, $J = 286.1$, 286.1, 286.1 Hz, CF$_3$), 113.9, 113.8, 73.2, 73.1, 71.4, 55.2, 55.1