Synthetic Studies toward Dideoxynojirimycin Derivatives *via* Dehydroamino Acid as a Key Intermediate

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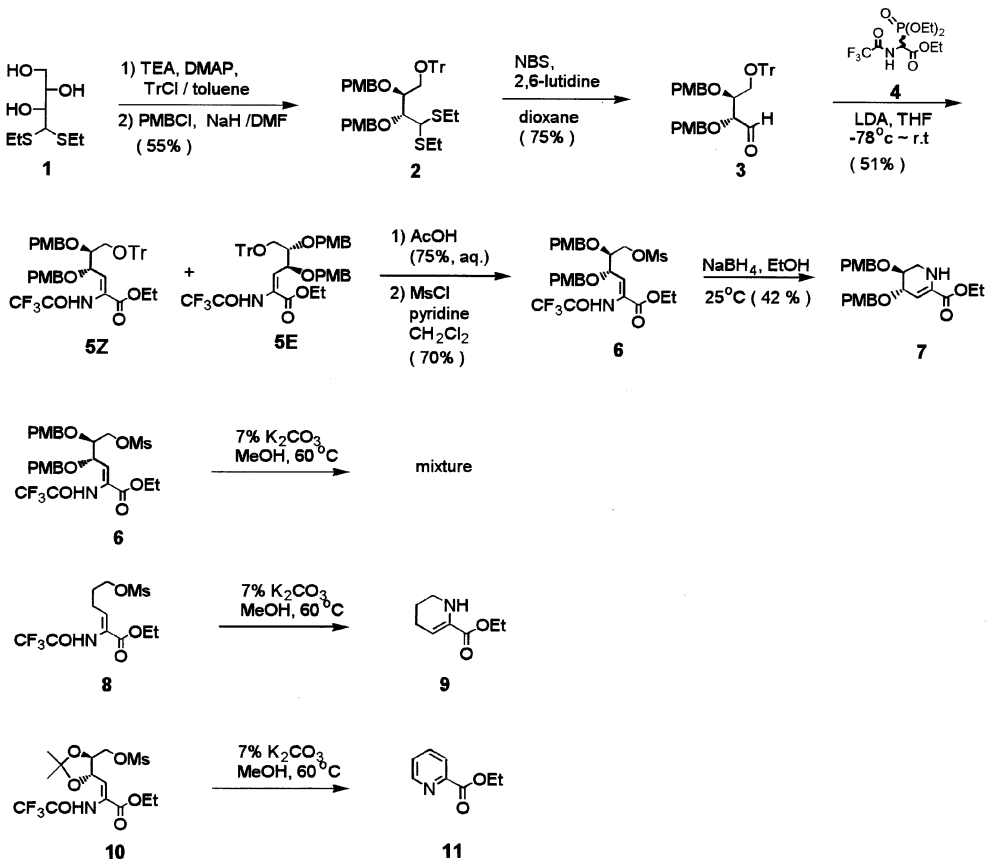
A number of natural glycosidase inhibitors and synthetic analogues were reported for potential therapeutic uses in diabetic mellitus,[1] tumor metastases,[2] and acquired immunodeficiency syndrome.[3] Development of improved synthetic methodologies for glycosidase inhibitors is still a challenging field. 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.

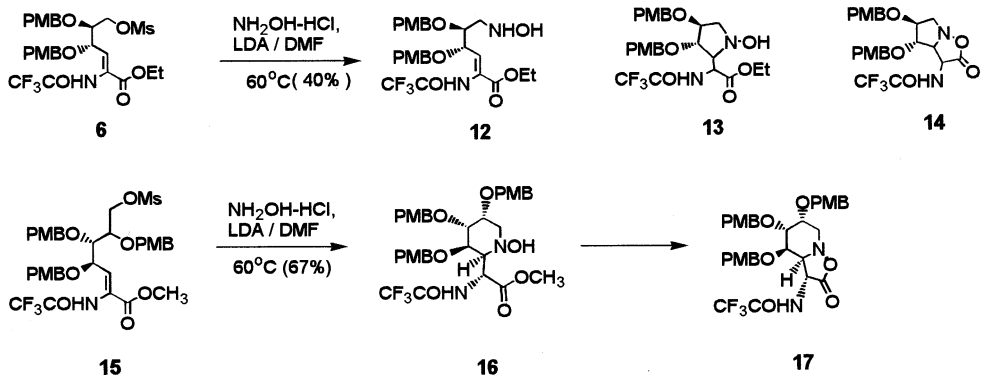
For the preparation of dehydroamino acid intermediate **5Z/E**, modified Horner-Emmons reaction between ethyl-phosphono-glycinate **4** and tetrose building block **3** gave the best result.[6] (Scheme 1) Ethyl-N-trifluoroacetyl-phosphono-glycinate **4** was prepared by free radical bromination of ethyl-N-trifluoroacetyl-glycinate 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 chrolide in pyridine.

At the beginning, spontaneous intramolecular cyclization



Scheme 1



Scheme 2

toward **7** was expected after removal of N-trifluoroacetyl protection group of **6** by treating K_2CO_3 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 K_2CO_3 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 $NaBH_4$ 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 hydrocholide 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 S_N2 reaction of hydroxylamine. (Scheme 2) It was an surprising result because another dehydroamino acid **15** was completely converted into a bicyclic 5-isoxazolidinone derivative **17** *via* piperidine derivative **16** under the same reaction condition.[9] 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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10. ^{1}H NMR and ^{13}C NMR of compound **7** were taken by Bruker AMX 500 MHz NMR, and spectral data are as following. ^{1}H NMR of **7** ($CDCl_3$): 7.18 (t, J = 8.88, 8.88 Hz, 4H, ArH) 6.87 (m, 4H, ArH), 6.35 (dd, J = 1.1, 3.7 Hz, 1H, vinyl-H), 4.46 (m, 4H, OCH_2Ar), 4.25 (td, J = 1.4, 7.1 Hz, 2H, OCH_2CH_3), 4.10 (d, J = 13 Hz, 1H, CH_2NH), 3.87 (m, 1H, CHOPMB) 3.81 (d, J = 2.48 Hz, 1H, $ArOCH_3$), 3.76 (m, 1H, CHOPMB), 3.41 (d, J = 13.4 Hz, 1H, CH_2NH), 1.37 (m, 3H, OCH_2CH_3); ^{13}C 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. ^{1}H NMR and ^{13}C NMR of compound **12** were taken by Bruker AMX 500 MHz NMR, and spectral data are as fol-

lowing. ^{1}H NMR of **12** ($CDCl_3$): 8.43 (s, 1H, CF_3CONH), 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_2Ar), 4.59 (m, 2H, OCH_2Ar), 4.30 (m, 4H, OCH_2Ar, OCH_2CH_3, CHOPMB), 3.80 (d, J = 2.8 Hz, 6H, $ArOCH_3$), 3.75 (m, 1H, CHOPMB), 3.65 (m, 1H, CH_2NH), 3.60 (m, 1H, CH_2NH); ^{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_2Ar), 4.51 (d, J = 11.61 Hz, 1H, OCH_2Ar), 4.51 (d, J = 3.91 Hz, 2H, OCH_2Ar), 4.43 (d, J = 11.31 Hz, 1H, OCH_2Ar), 4.39 (d, J = 11.30 Hz, 1H, OCH_2Ar), 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), 3.63 (dd, J = 3.91, 8.27 Hz, 1H, CH_2NO), 3.05 (brd, 1H, CH_2NO); ^{13}C NMR of **17**: 170.3, 159.7, 159.4, 159.1, 157.4 (ddd, J = 37.2, 37.2, 37.2 Hz, CF_3CO), 133.0, 130.1, 129.9, 129.6, 129.5, 129.3, 129.2, 129.0, 128.6, 115.3 (ddd, J = 286.1, 286.1, 286.1 Hz, CF_3), 113.9, 113.8, 73.2, 73.1, 71.4, 55.2, 55.1.