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Chiral Synthesis of Both Enantiomers of 1,4-Dideoxy-1,4-iminolyxitol and 1,4-Dideoxy-1,4-iminoribitol

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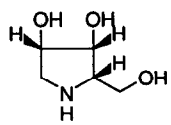
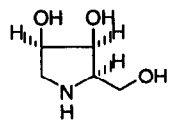
Abstract: Reaction of 2,3-dibromopropionyl chloride with 4-methoxyphenol and (S)-1-methylbenzylamine yielded a 4:5 mixture of readily separable diastereomeric aziridine esters in an excellent yield. Both diastereomers, upon heating with vinylene carbonate, furnished four readily separable diastereomeric pyrrolidine esters, respectively, which were transformed into both enantiomers of 1,4-dideoxy-1,4-iminolyxitol and 1,4-dideoxy-1,4-iminoribitol.

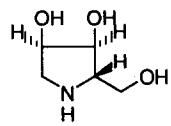
Despite of their small molecular size and less complexity, synthesis of polyhydroxylated pyrrolidines related to the glucosidase inhibitors[1] such as an α-mannosidase inhibiting naturally occurring swainsonine[2] has been practically not so easy to be carried out mostly owing to high polarity and water-solubility of the target molecules.[1,3,4,5] We report here a simple chiral approach to all possible isomers of *cis*-3,4-dihydroxyprolinols, L- and D-1,4-dideoxy-1,4-iminolyxitols[1,5] (**1**) and L- and D-1,4-dideoxy-1,4-iminoribitols[3,4] (**2**), by diastereomeric separation of the intermediates obtained by an intermolecular 1,3-dipolar cycloaddition which has been first employed in a non-chiral synthesis of a *N*-substituted 1,4-dideoxy-1,4-iminolyxitol.[6]



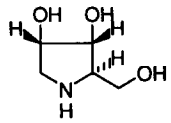
1,4-dideoxy-1,4-imino-L-lyxitol (L-**1**)



1,4-dideoxy-1,4-imino-D-lyxitol (D-**1**)



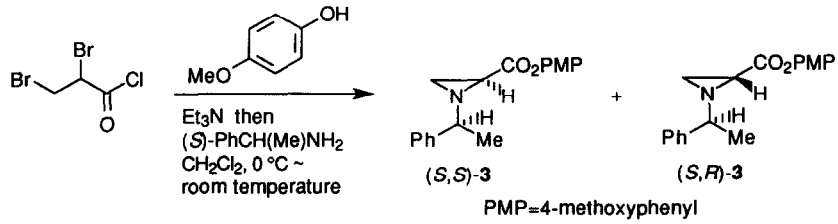
1,4-dideoxy-1,4-imino-L-ribitol (L-**2**)



1,4-dideoxy-1,4-imino-D-ribitol (D-**2**)

Figure 1

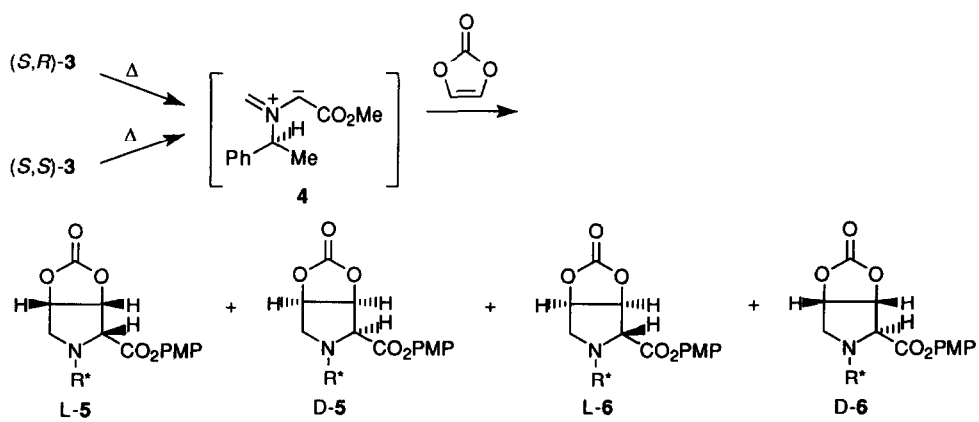
Reaction of 2,3-dibromopropionyl chloride with 4-methoxyphenol and (*S*)-1-methylbenzylamine in the same flask[7] afforded less polar (*S,S*)-aziridine [(*S,S*)-**3**], mp 78.5 - 79.0 °C, $[\alpha]_D^{27}$ –88.7 (*c* 0.85, $CHCl_3$), and more polar (*S,R*)-aziridine [(*S,R*)-**3**], mp 91.0 - 92.0 °C, $[\alpha]_D^{27}$ +121.6 (*c* 0.88, $CHCl_3$), in 43 and 51% yields after separation by silica gel column chromatography. Stereochemistry of the products could be determined unambiguously by transforming each into the known methyl ester[8] by methanolysis in the presence of potassium carbonate, respectively. Regardless of their chirality on the aziridine ring, both of the aziridines furnished a mixture of a pair of the same less polar adducts and a pair of the same more polar adducts in a good total yield in a 3:1 ratio on heating with three equivalents of vinylene carbonate in toluene in a sealed tube at 280 °C for 30 min, respectively. These reactions presumably proceed by generation of the same azomethine ylide (**4**)



Scheme 1

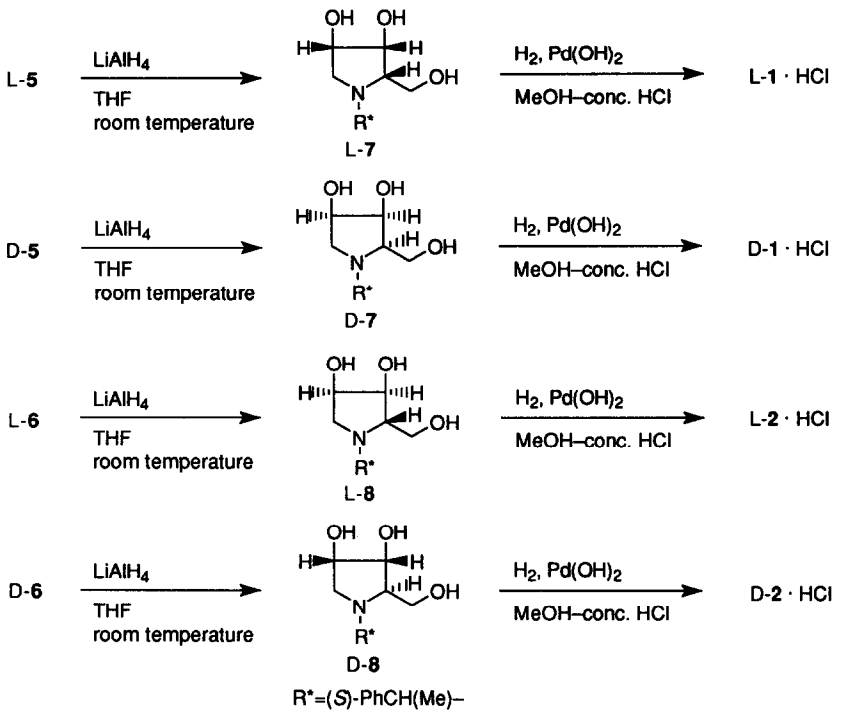
followed by low-diastereoselective and non-enantiospecific 1,3-dipolar cycloaddition with vinylene carbonate.[6,7] The all products could be separated by silica gel column chromatography to give the most polar (L-**5**), mp 140 - 141 °C, $[\alpha]_D^{27}$ +52.8 (*c* 0.43, $CHCl_3$), the next polar (D-**5**), mp 183.5 - 185.0 °C, $[\alpha]_D^{28}$ –239.4 (*c* 1.46, $CHCl_3$), the next least polar (D-**6**), mp 120.5 - 121.5 °C, $[\alpha]_D^{30}$ –128.7 (*c* 0.84, $CHCl_3$), and the least polar (L-**6**), mp 180 - 181 °C, $[\alpha]_D^{29}$ –4.4 (*c* 0.55, $CHCl_3$), isomers in yields of 30, 33, 11, and 10%.

The more polar pair was found to consist of all-*cis* diastereomers, (L-**5**) and (D-**5**). Thus, the most polar isomer (L-**5**) was first reduced with lithium aluminum hydride to give the *N*-substituted triol (L-**7**), $[\alpha]_D^{28}$ +10.6 (*c* 1.1, MeOH), in 71% yield. Removal of the *N*-substituent was achieved by hydrogenolysis to give 1,4-dideoxy-1,4-imino-L-lyxitol (L-**1**) hydrochloride, mp 162.5 - 163.5 °C, $[\alpha]_D^{29}$ –20.3 (*c* 0.28, H_2O) [lit.[5]: mp 155 - 156 °C, $[\alpha]_D^{20}$ –18.4 (*c* 0.22, H_2O)], in 83% yield. On the same treatment the next polar diastereomer (D-**5**) furnished the enantiomeric 1,4-dideoxy-1,4-imino-D-lyxitol (D-**1**) hydrochloride, mp 163.0 - 164.0 °C, $[\alpha]_D^{27}$ +20.3 (*c* 0.72, H_2O) [lit.: mp 157 - 159 °C[1a]: mp 159 - 161 °C,[1b] $[\alpha]_D^{20}$ +18.8 (*c* 0.16, H_2O)[1a]: $[\alpha]_D^{20}$ +19.8 (*c* 0.45, H_2O)[1b]], in 64% overall yield *via* the *N*-substituted triol (D-**7**), mp 85.0 - 85.5 °C, $[\alpha]_D^{28}$ –37.2 (*c* 0.41, MeOH). The D-enantiomer (**D-1**) has been reported to be a potent competitive inhibitor of α-galactosidase.[1a]



R*=(*S*)-PhCH(Me)–; PMP=4-methoxyphenyl

Scheme 2

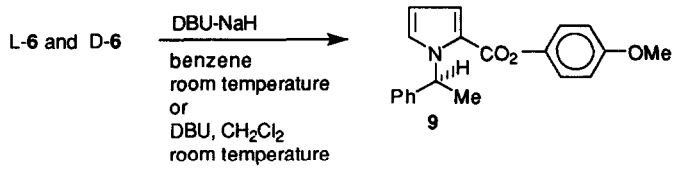


Scheme 3

The less polar pair, on the other hand, was concluded to be a diastereomeric mixture of the *trans*-1,2; *cis*-3,4-isomers, L-**6** and D-**6**. Thus, on the same sequential reduction and hydrogenolysis as for the polar pair, the least polar isomer (L-**6**) furnished 1,4-dideoxy-1,4-imino-L-ribitol (L-**2**) hydrochloride, mp 132.0 - 133.0 °C, $[\alpha]_D^{29}$ –59.5 (*c* 0.78, H_2O) [lit.[4]: mp 126 - 131 °C, $[\alpha]_D^{20}$ –59.0 (*c* 0.59, H_2O)], in 56% overall yield, *via* the *N*-substituted triol (L-**8**), $[\alpha]_D^{27}$ –8.9 (*c* 0.80, MeOH). On the same treatments, the next least polar isomer (D-**6**) afforded the enantiomeric 1,4-dideoxy-1,4-imino-D-ribitol (D-**2**) hydrochloride, mp 132.0 - 132.5 °C, $[\alpha]_D^{26}$ +59.0 (*c* 0.79, H_2O) [lit.[3]: mp 128 - 132 °C, $[\alpha]_D^{20}$ +57.6 (*c* 0.59, H_2O)], in 48% overall yield *via* the *N*-substituted triol (D-**8**), mp 120.5 - 122.0 °C, $[\alpha]_D^{26}$ –65.5 (*c* 0.51, MeOH).

An attempt to transform the polar pair made up of the all *cis*-isomers, (L-**5**) and (D-**5**), into the less polar pair made up of the thermodynamically more stable *trans*-2,3; *cis*-3,4-isomers, (L-**6**) and (D-**6**), could not be accomplished by employing the conditions which brought about facile epimerization of some 3,4-disubstituted proline esters in the synthesis of the kainoid amino acids.[9] Thus, exposure of the polar pair to a mixture of sodium hydride and DBU in benzene or DBU in dichloromethane furnished a complex mixture from which the *N*-substituted pyrrole (**9**), mp 112.0 - 112.5 °C, $[\alpha]_D^{28}$ –149.2 (*c* 0.72, $CHCl_3$), could be isolated in a low yield (~35%).

In conclusion, although the present synthesis employs most conventional diastereomeric separation, it can provide a highly simple way to all possible enantiomers of both D- and L-series of 1,4-dideoxy-1,4-iminolyxitol (**1**) and 1,4-dideoxy-1,4-iminoribitol (**2**) related to the glucosidase inhibitors.



DBU=1,8-diazabicyclo[5.4.0]undec-7-ene

Scheme 4

References and Notes

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