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AN ASYMMETRIC SYNTHESIS OF DIFFERENTIALLY PROTECTED *MESO*-2,6-DIAMINOPIMELIC ACID

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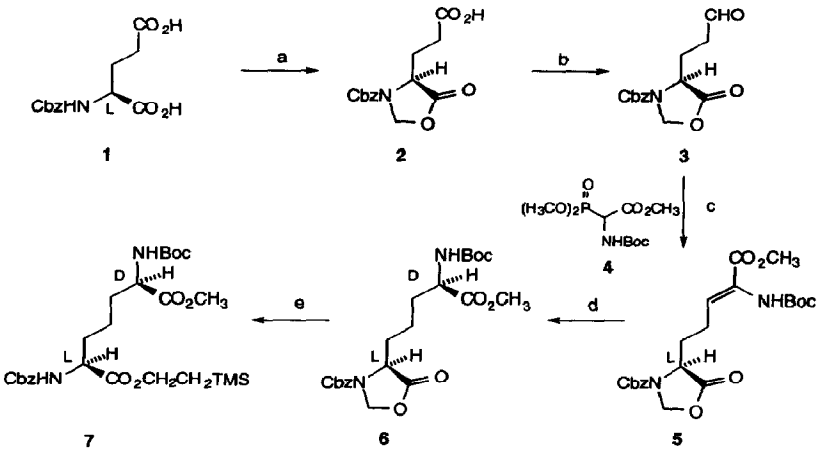
Abstract: Differentially protected meso-2,6-diaminopimelic acid, a component of bacterial cell walls, a biosynthetic precursor of L-lysine and a constituent of several synthetic immunostimulants, has been prepared stereospecifically from L-glutamic acid.

Diaminopimelic acid (DAP), a naturally occurring amino acid, plays an essential role in cell wall structure and microbial metabolism. The *meso* form is widely encountered as a cross-linking element of the peptidoglycan of most Gram-negative and some Gram-positive bacteria and aids in the binding of important macromolecules to the cell wall.[1] It is also a biosynthetic precursor of L-lysine through the action of *meso*-DAP decarboxylase,[2] except in mammals where this pathway is lacking and L-lysine must be included in the diet.[3] Inhibitors of the crucial enzymes in this pathway are potential antimicrobial and herbicidal agents which may display important selectivity and low mammalian toxicity.[4] In addition to their role in bacteria, *meso*-DAP and L,L-DAP are also components of several naturally occurring and synthetic immunostimulants derived from substructures of bacterial cell walls.[5]

The development of new therapeutic agents incorporating DAP requires the stereoselective synthesis of DAP derivatives. While a number of workers have reported on the synthesis and the enzymatic resolution of racemic DAP and its derivatives,[6] only recently have stereoselective syntheses appeared.[7] In one such synthesis by Jurgens, the two stereocenters were fixed using an oxazolidine derived from D-serine and applying the alkylation of an L-valine derived Schollkopf chiral glycine equivalent.[8] Williams and coworkers have reported the synthesis of the three diastereomers of DAP *via* the stereoselective alkylation of chiral oxazinone enolates.[9] We report herein the stereoselective synthesis of differentially protected *meso*-DAP by a procedure involving the catalytic asymmetric reduction of an acrylate intermediate derived from L-glutamic acid (Scheme 1).

The carboxylate group of the Cbz protected oxazolidinone **2**, prepared from Cbz protected L-glutamic acid (**1**),[10] was reduced with borane-dimethyl sulfide complex in THF with warming from 0 °C to room temperature. The reaction mixture was concentrated and treated directly with PCC in methylene chloride at room temperature, avoiding a hydrolytic aqueous workup and problems associated with trans-lactonization of the intermediate alcohol. The resulting aldehyde **3** was readily isolated and purified by flash chromatography, or used directly in the next step following a crude filtration through Celite.

Scheme 1



(a) $(CH_2O)_n$, toluene, Δ, 86 %; (b) (i) $BH_3{\cdot}SMe_2$ 0 -> 25 °C (ii) PCC 25 °C, 51% (2 steps) (c) KHMDS -78 -> 25 °C, 75% (d) H_2 (40 psi) $[Rh(NBD)_2]ClO_4$•(S,S)-chiraphos 25 °C, 80% (3:1 D:L) (e) $TMSCH_2CH_2OH$, LiHMDS 0 °C, 53%

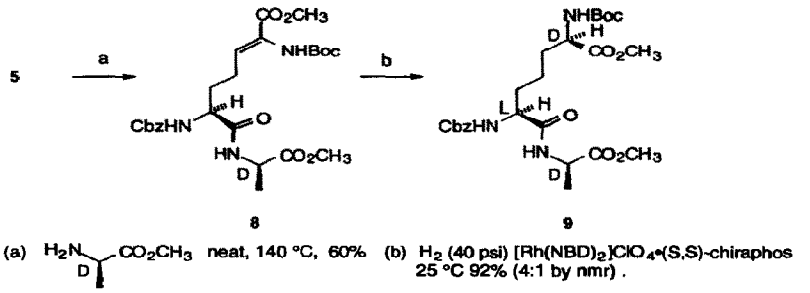
Homologation of the aldehyde with the potassium anion of amino phosphinate **4**,[11] generated by treatment with potassium bis(trimethylsilyl)amide in methylene chloride at -78 °C, provided the acrylate **5** as a mixture of isomers. The mixture was readily separated by flash chromatograpy to give a 6.4:1 ratio of the Z and E isomers, respectively. The Z isomer was subjected to catalytic hydrogenation using the chiral rhodium catalyst (S,S)-chiraphos $Rh(NBD)_2ClO_4$ in an 8:1 mixture of THF and acetic acid at 40 psi of hydrogen to give an inseparable mixture of diastereomers in a roughly 3:1 ratio based on nmr spectral analysis. From the work of Melillo and coworkers, the stereochemistry of the newly created center of the major isomer was assigned the D configuration shown for compound **6**.[12]

Direct hydrolysis of the oxazolidinone gave rise to an intractable mixture containing starting material and the carboxylic acid product. However, treatment of **6** with the lithium alkoxide of trimethylsilyl ethanol, generated from the alcohol and lithium bis(trimethylsilyl)amide, cleanly generated the ester **7** as a separable mixture of diastereomers. Purification using flash chromatography afforded the D,L product **7** as the major diastereomer in 53% yield. Overall, a *meso*-diaminopimelic acid derivative bearing orthogonal protection on all four functional groups was produced in 14% yield from L-glutamic acid.[13] Selective deprotection of **7** was readily accomplished through treatment with tetrabutylammonium fluoride in THF at room temperature for several hours to give the corresponding carboxylic acid quantitatively. This acid was utilized further in the development of novel peptidomimetics.

In an alternative approach outlined in Scheme 2, a dipeptide was prepared by first heating a neat mixture of the oxazolidinone **5** and the free base of D-alanine methyl ester to give **8.** Next, asymmetric hydrogenation under the conditions described above afforded the protected dipeptide **9** as a 4:1 ratio of diastereomers as evidenced by nmr spectroscopy. Multiple recrystallizations from ether with 10% THF provided the major diastereomer in 33% yield with greater than 95% purity. The x-ray crystal structure of this diastereomer

confirmed the assignment of the D configuration for the newly created center. This dipeptide was also utilized further in the preparation of novel therapeutic peptidomimetics.

Scheme 2



In conclusion, this synthesis is a flexible, stereoselective route for the preparation of differentially protected *meso*-DAP. In principle, the method also allows for the preparation of the L,L or D,D isomers of DAP depending on the choice of starting amino acid (L- or D-glutamic acid) and chiral rhodium catalyst (using the S,S-chiraphos or DIPAMP ligands). The utilization of this chemistry in the preparation of biologically active peptidomimetics will be reported in due course.

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13. All products were completely characterized (^{1}H, ^{13}C NMR, MS, IR, $[\alpha]^{D}$, combustion analysis or HRFAB) and shown to be consistent with the structures indicated.

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