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Asymmetric synthesis of differentially protected *meso*-2,6-diaminopimelic acid

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Abstract—*meso*-2,6-Diaminopimelic acid, an important linking component of bacterial cell walls and a biosynthetic precursor of L-lysine has been prepared differentially protected in a stereospecific manner from both L-aspartic and L-glutamic acid. The key step to establish the second chiral center involves the asymmetric reduction of a pyruvate moiety with Alpine-Borane®. *S*-2-Amino-6-oxopimelic acid, the hydrolyzed open chain form of tetrahydrodipicolinic acid, a biosynthetic precursor of *meso*-2,6-diaminopimelic acid, was also prepared via deprotection of the key pyruvate intermediate.

2,6-Diaminopimelic acid (DAP) is a naturally occurring amino acid found in both bacteria and higher plants. It is a symmetrical α,α′-diaminodicarboxylic acid and can therefore exist in three stereoisomeric forms. *meso*-DAP serves as the final precursor in the biosynthesis of L-lysine in both bacteria and higher plants[1] and is also an essential component of the peptidoglycan of most pathogenic bacteria (nearly all Gram-negative and most Gram-positive bacteria with the notable exception of *Staphylococcus aureus* where it is replaced by lysine).[2] It is involved as the nucleophilic component in the key peptide cross-linking step between two adjacent glycan strains. This is one of the final steps in peptidoglycan biosynthesis and not only defines the two- and three-dimensional structural array of the cell wall but also imparts structural rigidity and strength to it. In Gram-negative bacteria DAP serves the additional function of anchoring the outer membrane to the cell wall via the Braun lipoprotein.[2] Both LL-DAP and *meso*-DAP are also components of a number of immunostimulants derived from bacterial cell wall substructures.[3]

The DAP biosynthetic pathway has been well elucidated in *Escherichia coli*.[4] In this aspartate-derived biosynthetic pathway, L,L-DAP is converted to *meso*-DAP by the action of diaminopimelate epimerase. Because of its pivotal role in bacterial cell wall biosynthesis and function and the fact that *meso*-DAP is the precursor to the essential amino acid lysine, much interest has been generated in regulating or inhibiting the DAP biosynthetic pathway. Since DAP is not a constituent of animal tissue and the DAP biosynthetic pathway is absent in mammals, then inhibitors of the diaminopimelate pathway have a good chance of displaying low toxicity toward the mammalian host. Therefore inhibition of either DAP biosynthesis or its utilization affords an attractive target for antibacterial chemotherapy.

The development of inhibitors of the DAP pathway requires the stereoselective synthesis of analogs and derivatives of DAP. In spite of the apparent simplicity of this amino acid, it is only in recent years that stereochemically unambiguous syntheses of *meso*-DAP or L,L-DAP and their analogs have been reported in the published literature.[5–11] The establishment of the requisite chiral centers in these syntheses fall into three general categories; the use of chiral auxiliaries, the coupling of two fragments derived from the chiral pool, or the asymmetric reduction of an intermediate with one chiral center already established. The latter is exemplified by a number of stereoselective syntheses[7b,8,9] of differentially protected *meso*-DAP, involving the catalytic asymmetric reduction of an amino-acrylate intermediate derived from L-glutamic acid. In this paper we describe our complementary approach to the asymmetric synthesis of differentiated *meso*-DAP and related compounds.

Conceptually, the approach we describe utilizes one chiral center from the 'chiral pool' in the form of either aspartic acid (Scheme 1) or glutamic acid (Scheme 2), and introduces the other chiral center via Alpine-

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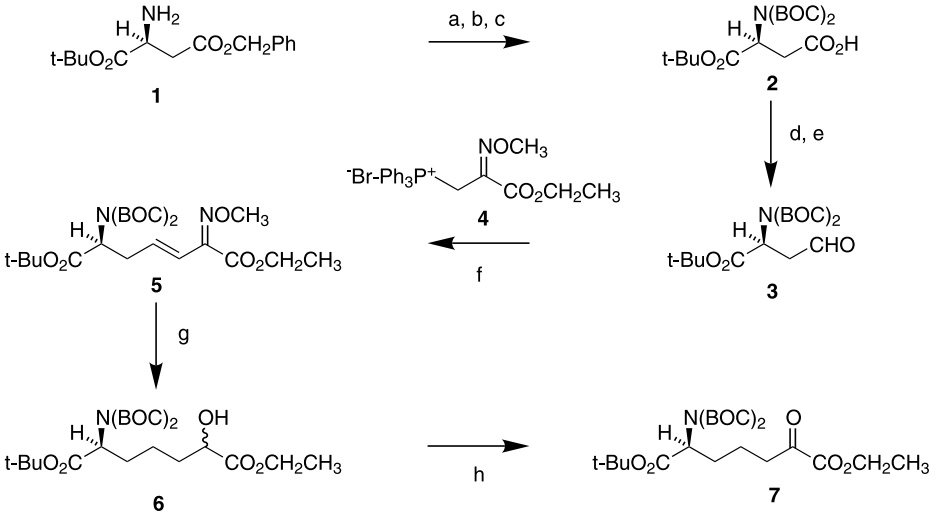
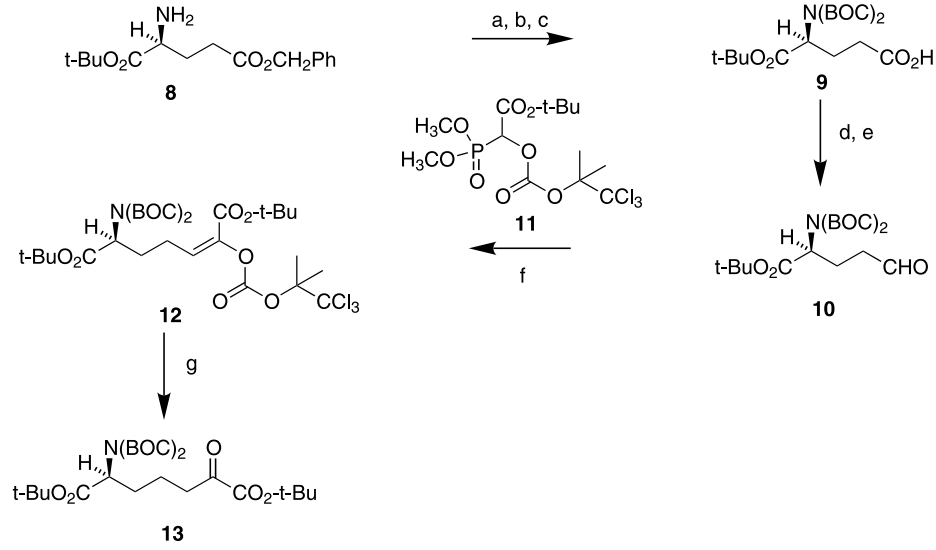


Scheme 1. (a) BOC_2O, CH_2Cl_2, cat. DMAP, 95%; (b) BOC_2O, 1 equiv. DMAP, CH_3CN, 24 h, 90%; (c) 10% Pd–C, H_2, CH_3OH, 100%; (d) $BH_3{\cdot}(CH_3)_2S$, THF, 100%; (e) $CrO_3{\cdot}(Py)_2$, CH_2Cl_2, 85%; (f) **4**, K_2CO_3, DMF, 92%; (g) 10% Pd–C, H_2O–HOAc (1:9), 45%; (h) $CrO_3{\cdot}(Py)_2$, CH_2Cl_2, 65%.

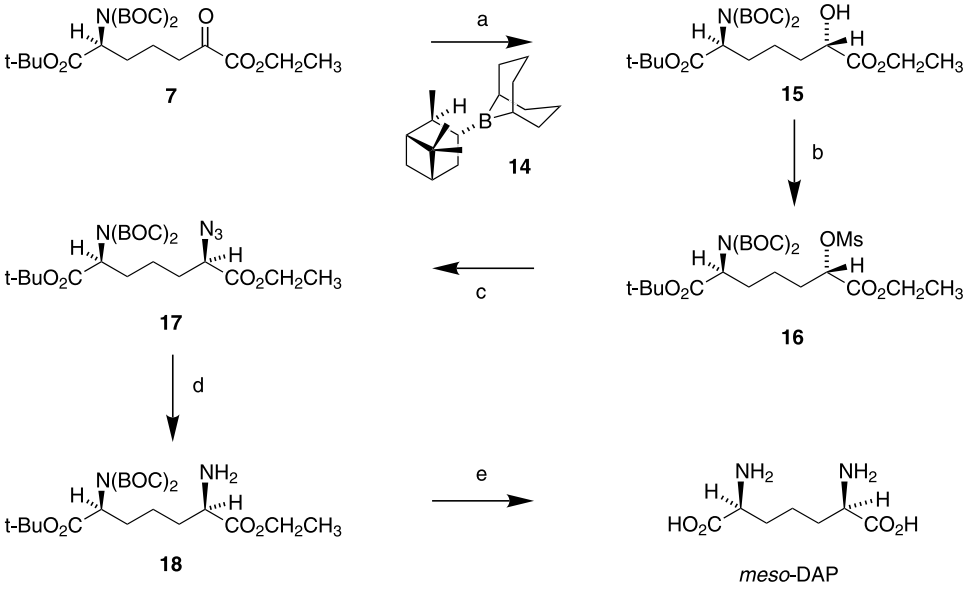


Scheme 2. (a) BOC_2O, Et_3N, CH_2Cl_2, 93%; (b) BOC_2O, 1 equiv. DMAP, CH_3CN, 24 h, 94%; (c) 10% Pd–C, H_2, THF, 100%; (d) $BH_3{\cdot}(CH_3)_2S$, THF, 100%; (e) PCC, CH_2Cl_2, Celite, 85%; (f) **11**, LiHMDS, THF, −78°C, 86%; (g) Zn, HOAc, Et_2O, +10°C, 90%.

Borane®[12] reduction on the keto-moiety of a pyruvate ester[11b] (Scheme 3).

As shown in Scheme 1, the readily available aspartate diester, **1**, was treated with di-*t*-butyldicarbonate to form the mono-*t*-BOC protected derivative and a second *t*-BOC protecting group was then introduced under more forcing conditions (*t*-BOC_2O, 1 equiv. DMAP, CH_3CN, rt, 24 h, 90%). Removal of the C-4 benzyl-protecting group by catalytic hydrogenation afforded the acid **2** in an overall yield of 86% from **1**. The acid, **2** was then converted to the aldehyde, **3**, via the corresponding alcohol, in a routine two step reduction–oxidation sequence. Application of this same chemistry to the glutamic acid series (Scheme 2) afforded the corresponding C_5-aldehyde, **10**, in an overall yield of 74% from **8**. Protection with two BOC groups was adopted to permit the use of the more convenient diborane reduction sequence (rather than a borohydride reduction of the mixed anhydride that is used when only mono-BOC protection is used). In addition the mono-BOC protected aldehydes corresponding to aldehydes **3** and **10**, are relatively unstable, with the C_5 series rapidly cyclizing to the aminal which is then often reluctant to undergo further reactions. Aldehydes **3** and **10** on the other hand are relatively stable and can be stored in the freezer for months without any loss of reactivity.

Condensation of the aldehyde **3**, with the stabilized phosphorane three carbon synthon, **4**,[13] afforded the corresponding unsaturated oxime ester, **5**, in a 92% yield. This compound served as a versatile intermediate to a variety of DAP analogs, since one can selectively



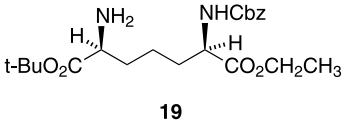
Scheme 3. (a) *R*-(+)-Alpine-Borane® (**14**), made in situ from *R*-(+)-α-pinene and 9-BBN, CH_2Cl_2, 86%, *S*:*R*=94:6; (b) MsCl, Py, 1 equiv. DMAP, CH_2Cl_2, 100%; (c) NaN_3, DMF, 100%; (d) 10% Pd–C, H_2, 100%, *R*:*S*=93:7; (e) 2.5N HCl, Δ, 100%.

reduce the oxime and the olefinic moieties.[13] Hydrogenation of **5** in aqueous acetic acid, afforded the corresponding hydroxy ester, **6**, in 45% yield which was then oxidized to the pyruval ester, **7** in 60% yield (conditions for these two steps were not optimized). In a complimentary approach depicted in Scheme 2, the C5 aldehyde, **10** underwent a facile Horner–Wadsworth–Emmons reaction with the trichlorobutyloxycarbonyl(TCBOC)-protected oxygenated phosphonate, **11**,[14] to afford the enol ester **12**, in an 86% yield with an *E*:*Z* ratio of 8:1. Reductive elimination of the TCBOC protecting group with zinc dust in a dilute solution of acetic acid in ether, unmasked the pyruval ester function to give **13,** the corresponding *t*-butyl ester analog of **7**.

Treatment of the pyruval ester **7** with *R*-(+)-Alpine-Borane®, **14**,[12] afforded the desired *S*-hydroxy ester, **15** [*S*:*R*=94:6]. The stereochemical outcome of this reduction was determined by ^{19}F NMR analysis of the Mosher esters[15] of **15** in comparison to the corresponding diastereomeric mixture of Mosher esters from **6**. The alcohol was converted to the corresponding *R*-azido ester, **17** (via the mesylate, **16**), and then converted to the corresponding *R*-amino ester, **18** [*R*:*S*=93:7] by catalytic hydrogenation. The stereochemical outcome of the sequence was determined by ^{19}F NMR analysis of the corresponding Mosher amides.[15] Protection of the free amino group in **18** as the Cbz followed by selective removal of the two BOC groups from the amine at the other end of the pimelic acid chain afforded **19**. This compound was utilized for Mosher amide determination of the stereochemical integrity of the other chiral center in the molecule. ^{19}F NMR analysis showed that no racemization had occurred at this center for any step during the entire synthetic sequence.

Another useful application of this chemistry has been its application to the synthesis of a number of substrates for the enzymes of the DAP biosynthetic pathway. Tetrahydrodipicolinic acid, **20**, the natural substrate for the succinyl-transferase in the DAP pathway has not been available optically active and is rather unstable in aqueous solution.[16] A form of tetrahydrodipicolinic acid that can be isolated and characterized was required to help set up an assay for the reductase and succinylase enzymes. Hydrolysis of **7** with 1N NaOH in THF afforded the corresponding pyruvic acid analog, **21**, which was deprotected under anhydrous conditions to afford the stable amino pyruvate **22** as the TFA salt (Scheme 4). On dissolution in assay buffer, **22** establishes an equilibrium mixture containing the open form (**22**) and the ring closed tetrahydrodipicolinic acid, **20** (via **23**).

In summary, this synthesis provides a flexible, stereoselective route for the preparation of differentially protected *meso*-DAP and analogs. The approach, in principle also allows for the preparation of the corresponding D,D- or L,L-DAP isomers and analogs depending on the choice of starting amino acid [L or D] and the Alpine-Borane® [*R* or *S*] used. Furthermore, the procedure provides a variety of versatile intermediates amenable for further elaboration.



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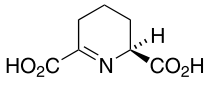

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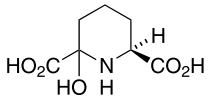

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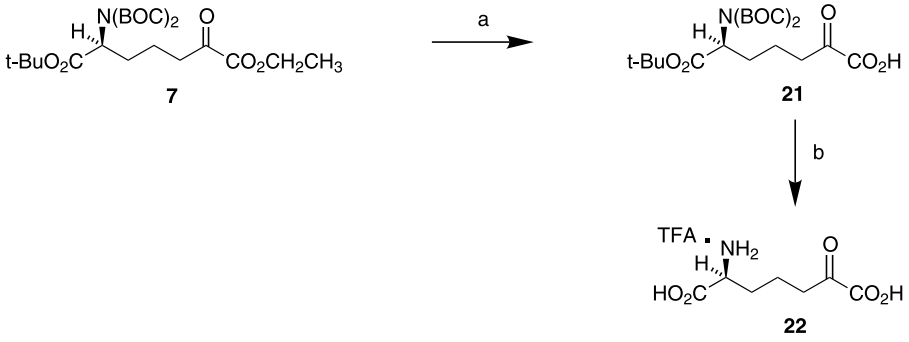

Scheme 4. (a) 1N NaOH, aqueous THF, 100%; (b) TFA, CH_2Cl_2, 100%.

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