Tetrahedron Letters, Vol. 33, No. 33, pp. 4727-4730, 1992
Printed in Great Britain

0040-4039/92 $5.00 +
Pergamon Press Ltd

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

Alex R. Jurgens

Chemical Process Research and Development, American Cyanamid Company, Medical Research Division, Lederle Laboratories, Pearl River, New York 10965

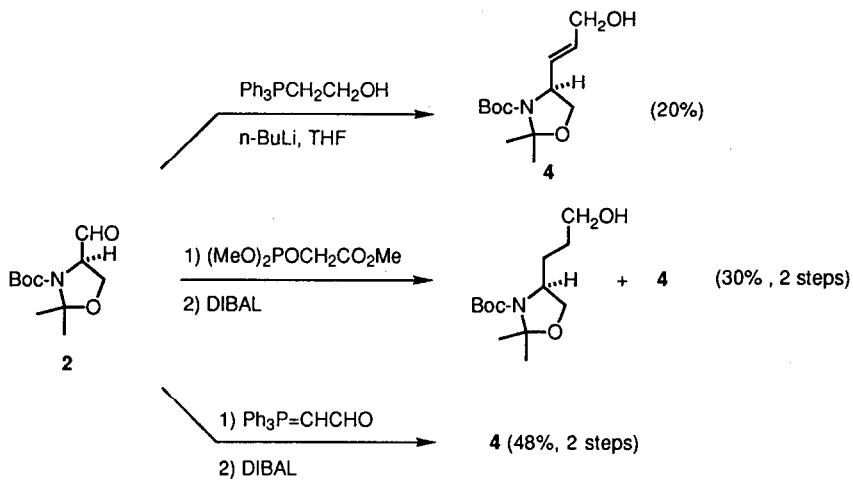
Abstract: *The synthesis of differentially protected meso-1,6-diaminopimelic acid, an important constituent of bacterial cell walls and the immediate biosynthetic precursor of L-lysine, has been accomplished in a completely stereospecific manner from D-serine.*

1,6-Diaminopimelic acid (DAP) is a cross linking unit of the cell wall peptidoglycan of most Gram-negative and some Gram-positive bacteria.[1] The most common of the three possible DAP stereoisomers, *meso*-DAP, is the direct biosynthetic precursor to lysine through the action of the enzyme *meso*-DAP decarboxylase.[2] Mammals lack this enzyme system and require a dietary source of lysine, thus inhibitors of this pathway represent possible antimicrobial agents with selective toxicity. The synthesis of DAP-containing peptides or peptidomimetics requires a supply of differentially protected *meso*-DAP in which the D- and L-termini can be selectively deprotected. When this work was initiated there were no stereospecific chemical syntheses of DAP in the literature. A published method[3], based on some older literature,[4] for preparation of differentially protected *meso*-DAP that relied on fractional crystallizations and enzymatic resolution was the only available method for preparation of these compunds. A number of syntheses of racemic DAP and derivatives have been published in the last few years,[5] most dealing with use as antibacterial agents. Several recent papers have demonstrated elegant stereospecific syntheses of substituted DAP derivatives. Bold[6] has synthesized a β-hydroxy DAP, Gelb and Vederas[7] have prepared β-fluoro DAP and Williams[8] has reported the α-hydroxymethyl DAP. Despite all of this activity in the area there still does not exist a practical stereospecific synthesis of a differentially protected *meso*-DAP.

The versatile, D-serine derived, Garner oxazolidine[9] (**2**, Scheme I) was chosen as a synthon. This material is produced in high yield and in very high enantiomeric excess. Most importantly, for a serinal equivalent it is shown to be configurationally stable. These chiral oxazolidines are seeing increasing utility as starting materials for the synthesis of amino alcohol and α-amino acid targets.[10] The strategy called for a two carbon homologation of the oxazolidine to an intermediate, such as **5**, which could be stereospecifically alkylated with the Schollkopf,[11] L-valine derived, chiral glycine equivalent (**6**). This would then provide the intact carbon framework in a stereocontrolled manner for final elaboration to product. The synthesis of the key intermediate

alcohol **4**, was undertaken using several different strategies (Figure I). An attempt to prepare **4** directly in one step *via* a Wittig reaction of the aldehyde with (2-hydroxyethyl)triphenylphosphonium bromide, according to the procedure of Kitahara,[12] was only moderately successful, giving the product alcohol[13] in only 20% isolated yield. Alternately, Horner-Emmons reaction of the aldehyde with trimethylphosphonoacetate gave an excellent yield (80%) of the desired α,β-unsaturated ester.[10(b)] All attempts to effect selective reduction of the unsaturated ester to the allylic alcohol **4** were accompanied by formation of significant quantities of the saturated alcohol, regardless of solvent, temperature, or reducing agent. The most successful route to the allylic alcohol involved Wittig reaction of aldehyde **2** with (triphenylphosphoranylidene)acetaldehyde to provide the corresponding α,β-unsaturated aldehyde **3** (Scheme I) in high yield. A DIBAL reduction of the aldehyde then provided pure alcohol **4** in 48% yield for two steps from the aldehyde **2**, with only trace quantities of the corresponding saturated alcohol. In all above cases only the *E* olefin geometry was formed as determined from the ^{1}H NMR coupling constants ($EJ_{CH=CH}$ > 15 Hz).

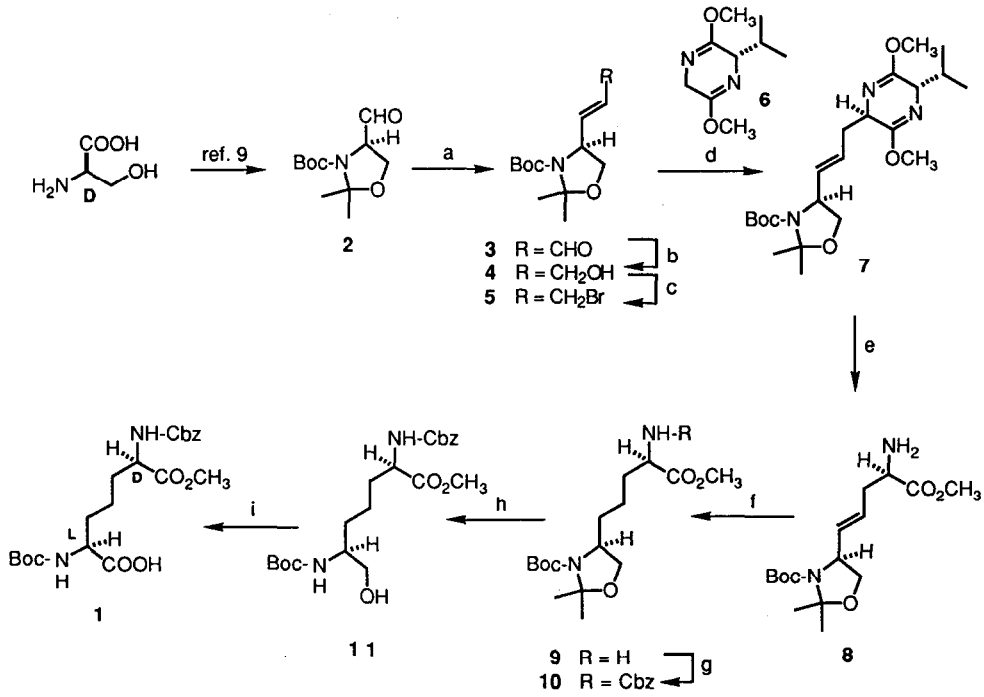
Figure I



Alcohol **4** could be readily converted to bromide **5** using CBr_4/triphenylphosphine.[14] The product bromide **5** underwent extremely facile alkylation with Schollkopf L-val-gly derived dihydropyrazine **6** to provide **7**, which contained the entire carbon framework and prerequisite stereochemistry for the target *meso*-DAP, in nearly quantitative yield. NMR spectral analysis[15] showed **7** to be a single chemical entity with no indication of formation of another diastereomer. Selective hydrolysis of dihydropyrazine **7** using mild acid conditions resulted in a modest yield of amino ester **8**. This yield, though, is comparable with those seen in the literature for related dihydropyrazine hydrolysis reactions.[11(b),16] Amino ester **8** could be isolated in pure form by careful column chromatography on silica gel or alternatively by controlled vacuum distillation of methyl valinate, the relatively volatile hydrolysis byproduct. Catalytic hydrogenation of the double bond was carried out in high yield using palladium on carbon and the product **9**, determined to be pure by ^{1}H and ^{13}C NMR, was used directly in the next step. Differential protection of the free amino group was accomplished as the CBZ derivative using standard

conditions to give intermediate oxazolidine **10** in excellent yield. Liberation of the L-terminus of the molecule was accomplished using the conditions of Wagner and Tilley,[10(a)] refluxing a wet methanolic solution of the oxazolidine with a catalytic amount of *p*-toluene sulfonic acid to give **11**. Finally, oxidation of the primary alcohol using pyridinium dichromate in DMF proved to be successful in providing pure **1** in 75% isolated yield.

Scheme I



(a) Ph_3P=CHCHO, toluene, Δ, 80%; (b) DIBAL, CH_2Cl_2, 0°, 60%; (c) Ph_3P, CBr_4, CH_2Cl_2, 0°, 95%; (d) *n*-BuLi, THF, -78°, 95%; (e) 0.1N HCl, THF, H_2O, 48%; (f) H_2/Pd/C, EtOAc, quant.; (g) Cbz-Cl, Et_2O, $NaHCO_3$, 84%; (h) *p*-TsOH, H_2O, CH_3OH, 91%; (i) PDC, DMF, 75%.

The stereochemical integrity of the process was determined by preparation of Mosher[17] esters of alcohols **4** and **11**. Analysis of the 300 MHz NMR spectra of these the esters showed the presence of only one diastereomer in each case, at the limit of detection, indicating enantiomeric purity ≥95%.

In conclusion this sequence represents a highly stereospecific route for preparation of differentially protected *meso*-DAP. In theory, the method will allow for the preparation of D,D- or L,L-DAP by simply varying either the oxazolidine (starting from L-serine) or the Schollkopf dihydropyrazine (starting from D-valine). In addition this procedure provides intermediates amenable for structural elaboration, should derivatives of the parent compound be required.

Acknowledgements. The author wishes to thank Professor M.F. Semmelhack and the American Cyanamid Co. for providing a Post-doctoral fellowship and Drs. Steven Schow and S. Ayral-Kaloustian for helpful discussions.

References and Notes

1. Patte, J.-C. In *Amino Acids: Biosynthesis and Genetic Regulation*; Hermann, K.M., Somerville, R.L., Eds.; Addison-Wesley: Reading, MA, 1983; pp 213-228.

2. Gottschalk, G. *Bacterial Metabolism*; Springer-Verlag: New York, 1979.

3. Anantharamaiah, G.M.; Roeske, R.W. In *Peptides: Synthesis-Structure-Function, Procedings of the Seventh American Peptide Symposium*, Rich, D.H., Gross, G., Eds.; Pierce Chemical Company, Rockford, Illinois, 1981; pp 45-47.

4. (a) Work, E.; Birnbaum, S.M.; Winitz, M.; Greenstein, J.P. *J. Am. Chem. Soc.* **1955**, *77*, 1916. (b) Wade, R.; Birmbaum, S.M.; Winitz, M.; Koegel, R.J.; Greenstein, J.P. *J. Am. Chem. Soc.* **1957**, *79*, 648.

5. (a) Kelland, J.G.; Arnold, L.D.; Palcic, M.M.; Pickard, M.A.; Vederas, J.C. *J. Biol. Chem.* **1986**, *261*, 13216. (b) Girodeau, J.-M.; Agouridas, C.; Masson, M.; Pineau, R.; Le Goffic, F. *J. Med. Chem.* **1986**, *29*, 1023. (c) Lam, L.K.P.; Arnold, L.D.; Kalantar, T.H.; Kelland, J.G.; Lane-Bell, P.M.; Palcic, M.M.; Pickard, M.A.; Vederas, J.C. *J. Biol. Chem.* **1988**, *263*, 11814. (d) Baumann, R.J.; Bohme, E.H.; Wiseman, J.S.; Vaal, M.; Nichols, J.S. *Antimicrob. Agents Chemother.* **1988**, *32*, 1119. (e) Bohme, E.H.; Gerhart, F.; Higgins, W. U.S. Patent 4,730,006, 1988.

6. Bold, G.; Duthaler, R.O.; Riediker, M. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 497.

7. Gelb, M.H.; Lin, Y.; Pickard, M.A.; Song, Y.; Vederas, J.C. *J. Am. Chem. Soc.* **1990**, *112*, 4932.

8. Williams, R.M.; Im, M.-N.; Cao, J. *J. Am. Chem. Soc.* **1991**, *113*, 6976.

9. (a) Garner, P.; Park, J.M. *J. Org. Chem.* **1987**, *52*, 2361. (b) Garner, P.; Park, J.M. *Org. Syn.* **1991**, *70*, 18.

10. (a) Wagner, R.; Tilley, J.W. *J. Org. Chem.* **1990**, *55*, 6289. (b) Beaulieu, P.L.; Duceppe, J.-S.; Johnson, C. *J. Org. Chem.* **1991**, *56*, 4196. (c) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*, Pergamon Press: New York, 1989.

11. (a) Schollkopf, U.; Groth, U.; Deng, C. *Angew. Chem. Int. Ed. Eng.* **1981**, *20*, 798. (b) Schollkopf, U.; Tiller, T.; Bardenhagen, J. *Tetrahedron* **1988**, *44*, 5293.

12. Kitahara, T.; Horiguchi, A.; Mori, K. *Tetrahedron* **1988**, *44*, 4713.

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

14. Kocienski, P.J.; Cernigliaro, G.; Feldstein, G. *J. Org. Chem.* **1977**, *42*, 353.

15. The NMR spectra of these oxazolidines was complicated by the presence of long-lived rotamers,[10(a)] this could be overcome by running spectra at 75°C in $CDCl_3$.

16. See for example: Boger, D.L.; Yohannes, D. *J. Org. Chem.* **1990**, *55*, 6000.

17. Dale, J.A.; Dull, D.L.; Mosher, H.S. *J. Org. Chem.* **1969**, *34*, 2543.

(Received in USA 14 April 1992)