Synthesis of 2,6-diaminopimelic acid (DAP) and its analogues

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This article concerns synthesis of 2,6-diaminopimelic acid, an important amino acid biosynthesized by bacteria and higher plants. A number of peptidoglycan fragments containing the diaminopimelic acid (DAP) residue exhibit antitumor and/or immunostimulant activity. DAP is a versatile building block of many natural and synthetic compounds with a number of potential medicinal applications. The synthesis of immunostimulants FK-156 and FK-565 is also presented.

Key words: diaminopimelic acid, DAP, *meso*-DAP, diaminodicarboxylic acids, synthesis, immunostimulants

Abbreviations: Ac – acetyl; 9-BBN – 9-borabicycyclo(3.3.1)nonane dimer; Bn – benzyl; Boc – *tert*-butoxycarbonyl; BOP – 1-benzotriazolyloxy-tris-dimethylamino-phosphonium hexafluorophosphate; *t*-Bu – *tert*-butyl; Cbz – benzyloxycarbonyl; *m*-CPBA – *m*-chloro-perbenzoic acid; CSA – camphor-10-sulfonic acid; DCM – dichloromethane; DEPBT – 3-(diethoxyphosphoryloxy)-3H-benzo[d][1,2,3]triazin-4-one; DIBAL – diisobutylaluminum hydride; DIEA – diethylamine; DIPEA – diisopropylethylamine; DMAP – 4-dimethyl-aminopyridine; DPPA – diphenylphosphoryl azide; Fmoc – 9-fluorenylmethoxycarbonyl; HBTU – *O*-(1H-benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetra-fluorophosphate; HMPA – hexamethylphosphoramide; HOBt – 1-hydroxybenzotriazole; IL-12 – interleukine 12; IFN-γ – interferon-γ; (*R*)-MTPA-Cl – (*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl

chloride; PDC – pyridinium dichromate; PyBOP – 1-benzo-triazoloxy-tris-pyrrolidino-phosphonium hexafluorophosphate; TEMPO – 2,2,6,6-tetramethyl-1-piperidinyloxy; TFA – trifluoroacetic acid; TMSE – trimethylsilylethanol; TMS – trimethylsilyl; Tolyl – *p*-toluene; Tr – trityl; Troc – 2,2,2-trichloroethoxycarbonyl; Ts – 4-toluenesulfonyl; Z – benzyloxy-carbonyl.

Diaminodicarboxylic acids contain two chiral carbons, two chemically identical amino and two carboxylic groups. They play crucial role in biology, biochemistry and organic chemistry, e.g. diaminoglutaric acid complexed with platinum demonstrates antitumor activity, diaminoadipic acid is an inhibitor of bacterial growth, and its *meso*-form is an important component of some medicinal compounds [1,2]. α,β-Diamino acids constitute a structural element in antibiotics, such as capreomycins, antrimycin, and lavendomycin [3]. Diaminosuccinic acid has been isolated from *Streptomyces rimosus* [(+)-(*S*,*S*)-diastereomer acid]. Several studies support its possible use as a ligand for aspartate-dependent enzymes that might be of interest for tumor therapy [3]. The important role in bacterial α-amino acid biosynthesis plays (2*S*,6*S*)-diaminopimelic acid (LL-DAP) **1**, which is epimerized by LL-DAP epimerase to form *meso*-(2*S*,6*R*)-diaminopimelic acid (*meso*-DAP) **2** (Figure 1) [4]. Diaminopimelic acid, a natural amino acid was found as a constituent of the bacterial and fungal cell wall structure and ingredient of higher plants. The *meso* form is widely encountered as a cross-linking element of the peptidoglycan of most Gram-negative bacteria and a precursor of L-lysine, which is used for this purpose by many Gram-positive organisms [5,6]. In addition to their role in bacteria, *meso*-DAP and LL-DAP are also components of several naturally occurring and synthetic immunostimulants derived form substructures of bacterial cell walls.

Zeitler and Steglich [3] reported an efficient method for the preparation of diastereomerically pure, orthogonally protected diaminosuccinic acid derivatives starting from easily accessible olefinic glycine dimers. Avenoza *et al.* [7] described synthesis of *meso*-2,4-diaminoglutaric acid starting from Garner's aldehyde. The key step in this synthesis is hydrogenation of compound **3**, followed by oxidation and hydrolysis (Scheme 1). Tanaka *et al.* [8] presented stereospecific synthesis of differentially protected (2*S*,4*S*)-2,4-diaminoglutaric acid **15** (Scheme 2) suitable for incorporation into peptides. Hiebl *et. al.* [9] described enantioselective synthesis of 2,5-diaminoadipic acid (DAA), 2,7-diaminosuberic acid (DAS), and 2,8-diaminoazelaic acid (DAZ) with high optical purity and high yields based on asymmetric catalytic hydrogenation in the presence of a chiral catalyst Et-DuPHOS-Rh. 2,7-Diaminosuberic acid (DAS) has been used successfully as a substitute for cystine to prepare biologically active peptide hormone analogues with improved chemical stability, e.g. oxytocin and somatostatin analogues. One of these compounds, a nonapeptide with hematoregulatory activity, has demonstrated significant protection in animal models against bacterial, fungal, and viral infection and in bone marrow transplantation [9]. The diaminoadipic acid derivatives were also synthesized in good yields by electrolysis of *N,N*-diacyl-dehydroalanines [10].

In this paper I focus on DAP synthesis and its practical application for preparation new immunostimulants, antibiotics and herbicides.

SYNTHESIS OF DAP AND ITS ANALOGUES

The development of new therapeutic agents incorporating 2,6-diaminopimelic acids require the stereoselective synthesis of DAP and their analogues. The synthesis of stereoisomers of DAP is difficult and complicated [11-30]. In older literature preparation of differentially protected *meso*-DAP relied on fractional crystallization and enzymatic

resolution of racemic derivatives. It was the only available method for preparation of such compounds [11]. Later several other syntheses of racemic DAP and its derivatives were published [5]. In that papers also stereospecific syntheses of substituted DAP were demonstrated. Bold *et al.* [12] synthesized β-hydroxy DAP, Gelb *et al.* [13] prepared β-fluoro DAP and Williams *et al.* [14] reported the α-hydroxymethyl DAP synthesis. The last one is exemplified by a number of stereoselective syntheses of differentially protected DAP or *meso*-DAP, involving the catalytic asymmetric reduction of an amino-acrylate intermediate derived from L-glutamic acid. Most of these syntheses involve setting one of the two chiral centers by stereoselective substrate-directed reactions or the use of chiral reagents. Setting of the desirable chiral centers in the described syntheses fall into three general categories: the use of chiral auxiliaries, the coupling together of two chiral fragments, or the asymmetric reduction of an intermediate with one chiral center. Jurgens [11] presented method for the preparation of differentially protected *meso*-DAP **26** (Scheme 3), DD- or LL-DAP by simply varying either the oxazolidine (starting from D-serine) or the Schöllkopf dihydropyrazine (starting from L-valine). Willams and Yuan [15] reported the synthesis of the three diastereomers of DAP *via* the stereoselective alkylation of chiral oxazinone enolates and (*S*,*S*)-2,7-diaminosuberic acid. For example, the synthesis of (*R*,*R*)-DAP **34** is detailed in Scheme 4. Both these methods seem to be expensive and troublesome. Holcomb *et al.* [5] described asymmetric synthesis of differentially protected *meso*-2,6-diaminopimelic acid from L-glutamic acid (Scheme 5). The carboxylate group of the Cbz protected oxazolidinone **36**, prepared from protected L-glutamic acid **35**, was reduced with borane-dimethyl sulfide complex in THF. The reaction mixture was then treated with PCC in methylene chloride to give aldehyde **37**. This aldehyde with compound **38** provided the acrylate **39** as a mixture of isomers. The Z isomer separated by flash chromatography was catalytically hydrogenated using the chiral rhodium catalyst (*S*,*S*)-chiraphos $Rh(NBD)_2ClO_4$ to give compound **40**.

Treatment of **40** with the lithium alkoxide of trimethylsilyl ethanol generated the ester **41**. Selective deprotection of compound **41** was readily accomplished through treatment with tetrabutylammonium fluoride in THF to give the corresponding carboxylic acid quantitatively. This acid was utilized further in the development of novel peptidomimetics.

Arakawa *et al.* [1] reported the stereospecific synthesis of the *meso*-diaminodicarboxylic acids, also *meso*-DAP, applying Diels-Alder adducts **43** *via* the cyclic hydrazodicarboxylic acids **45** (Scheme 6). The Diels-Alder adducts **43** derived from azodibenzoyl and cyclic dienes were oxidized by ruthenium tetroxide (RuO_4) to afford *cis*-dicarboxylic acids. Esterification of the dicarboxylic acids by diazomethane or thionyl chloride-methanol gave dimethyl esters **44a-c**. Five- and six-membered cyclic hydrazodicarboxylic acids **45a,b** were easily obtained by hydrolysis of **44a** and **44b** with 6N HCl-AcOH. *N*-Benzoyl groups of compound **44c** were reduced by borane-dimethyl sulfide in THF to give di-*N*-benzyl compound **47c**, which was then debenzylated by hydrogenolysis with 20% $Pd(OH)_2/C$ and hydrolysed with 2N HCl to give compound **45c**. Hydrogenolysis of *cis*-hydrazodicarboxylic acids **45** gives *meso*-2,4-diaminoglutaric acid **46a**, *meso*-2,5-diaminoadipic acid **46b**, and *meso*-2,6-diaminopimelic acid **46c** [1]. Gao *et al.* [22] presented synthesis of selectively protected derivatives of *meso*-DAP using four approaches: olefin metathesis skeleton assembly, one reaction employing chiral 2-phenylcyclohexyl auxiliaries, stereospecific reduction of 2-keto-6-aminopimelic derivatives with Binap-rethenium catalyst, and a reaction using chiral copper oxazoline catalysts. Both the chiral phenylcyclohexyl auxiliary route and the stereospecific reduction successfully lead to the desired DAP derivatives, but the best isomer ratio (94:6) and the most facile method employed chiral copper catalyst for a condensation of compound **51** with methyl glyoxylate **52** (Scheme 7). Mitsunobu insertion of the nitrogen functionality then affords the target protected DAP derivatives. This synthetic

approach can be used not only to produce these compounds, but also other DAP analogues e.g. useful for enzyme mechanism and inhibition studies [22].

Sutherland *et al.* [26] described the synthesis unsaturated α-aminopimelic acids as potent inhibitors of *meso*-diaminopimelic acid (DAP) D-dehydrogenase. The authors prepared two nonproteinogenic amino acids **57** and **58** (Figure 2) using an S_H2' allylstannane coupling reaction and a Wittig reaction. Kinetic studies show these compounds to be reversible inhibitors of DAP dehydrogenase with K_i values of 5.3 (competitive) and 44 μM (noncompetitive), respectively.

Davis and Srirajan [23] reported a new strategy for the enantioselective synthesis of (2*S*,6*S*)-DAP and *meso*-DAP, based on the sulfinimine (*N*-sulfinyl imine)-mediated asymmetric Strecker synthesis (Scheme 8). Condensation of 5-(benzyloxy)pentanal **60** with (*S*)-(+)-**59** and $Ti(OEt)_4$ afforded sulfinimine (*S*)-(+)-**61**. The sulfinimine-mediated asymmetric Strecker synthesis involves the addition of ethylaluminum cyanoisopropoxide [EtAl(O-*i*-Pr)CN] to the sulfinimine **62**. Conversion of **62** to the *N*-tosyl amino nitrile **63** was readily accomplished without epimerization, by oxidation with 57% *m*-CPBA. Hydrolysis with MeOHxHCl gave the amino acid methyl ester **64** which was further protected to give **65**. Hydrogenation and oxidation gave aldehyde **67**. The sulfinimine **68** was prepared as previously described and treatment with EtAl(O-*i*-Pr)CN gave the nitrile **69**. Following separation of the diastereoisomers by chromatography, hydrolysis and removal of the *N*-tosyl group to give the product which was purified by ion-exchange chromatography affording LL-DAP **1**. *meso*-DAP **2** was prepared in a related fashion by condensing sulfinamide (*R*)-(-)-**59** with aldehyde **67** to give compound **71**. Cyanide **72** addition and hydrolysis gave *meso*-DAP **2**.

In 2002 Sutherland and Vederas [21] synthesized new analogues of diaminopimelic acid using radical decomposition of iodobenzene derivative **75a** followed by decarboxylation and subsequent conjugate addition with selectively protected dehydroamino acids.

Diacyloxyiodobenzene **75** with dehydroamino acid BnO_2C-C(NHTr)=CH_2 give compounds **76**. Chiral hydrogenation of an unsaturated derivative **76** gives selectively-protected *meso*-DAP **78** (Scheme 9).

Kubasch and Schmidt [27] described synthesis muramyl- and 1,6-anhydromuramyl-, di-, tri- and tetrapeptides containing *meso*-diaminopimelic acid. The key step of the synthesis was obtaining unsymetrically derivatives of *meso*-diaminopimelic acid. *N*-Benzyloxycarbonyl-L-glutamate **79** was transformed into the oxazolidinone **80** which furnished aldehyde **81** after reduction of the carboxylate group and periodinane oxidation of the alcohol intermediate. This aldehyde **81** could be also obtained from acid chloride **82** by reduction with $LiAl(OtBu)_3H$ (Scheme 10). In Wittig-Horner reaction of aldehyde **81** with the phosphoryl glycine derivative **83**, in the presence of potassium hexamethyldisilazane (KHMDS) as a base, afforded a mixture of (*Z,E*)-**84**. Asymmetric hydrogenation of oxazolidinone derivatives (*Z*)-**84** with a rhodium catalyst and (*S,S*)-chiraphos provided a 3:1 mixture of (*S,R*)- and (*S,S*)-**85**. While, a simple catalytic hydrogenation with Wilkinson's catalyst gave a 3:2 mixture of diastereoisomers (*S,R*)-**85** and (*S,S*)-**85**. Treatment of this mixture with trimethylosilylethanol in presence of heksamethylsilazane lithium (LiHMDS) as base afforded diastereoisomers (*S,R*)-**86** and (*S,S*)-**86**, which could be separated by medium-pressure liquid chromatography (MPLC) and used for the synthesis of compared muramylpeptides [27].

Wang *et al.* [18] described efficient synthesis of the (2*S*,6*S*)- and *meso*-DAP via asymmetric hydrogenation of compounds **87** using [Rh(I)(COD)-(*S,S*) or (*R,R*)-Et-DuPHOS)]$^+$OTf$^-$ (Scheme 11). Collier *et al.* [19] reported stereoselective synthesis of *meso*-DAP using coupling of the organoboran homoalanine equivalent **90** with compound **91** (Scheme 12). In 2002 Collier *et al.* [20,28] reported that organoborane reagents **90**, which are readily available from serine, undergo efficient palladium-catalyzed Suzuki coupling reactions under mild conditions and with wide functional group tolerance. The adducts can be easily transformed

into a range of known and novel nonproteinogenic amino acids, including *meso*-DAP, (*R*,*R*)-DAP, and (*R*,*R*)-DAS, in enantiopure form.

Roberts and Chan [25] presented asymmetric synthesis of differentially protected *meso*-DAP where the key step to establish the second chiral center involved the asymmetric reduction of a pyruvate moiety with Alpine-Borane (Scheme 13). Treatment of the pyruval ester **96** with (*R*)-(+)-Alpine-Borane **97**, afforded the desired (*S*)-hydroxy ester **98** (*S*:*R* = 94:6). The alcohol was converted to the corresponding (*R*)-azido ester **99** (via the mesylate), and then converted to the (*R*)-amino ester, **100** (*R*:*S* = 93:7) by catalytic hydrogenation. The compound **100** after deprotection with 2.5N HCl gives *meso*-DAP **2**. This synthesis provides a flexible, stereoselective route for the preparation of differentially protected *meso*-DAP and analogs. This approach also allows preparation of the corresponding D,D- or L,L-DAP isomers and their analogs depending on the choice of starting amino acid [L or D] and the Alpine-Borane [*R* or *S*] used [25].

New peptides containing the 2,6-DAP skeleton and a system based on a proline residue fused to a diketopiperazine ring **101**, **102**, **103** (Figure 3) were described by Galeazzi *et al.* [29]. The authors synthesized peptide-like structures because some natural products, containing a 6,5-fused ring system [30], exhibit a wide range of biological activity (for instance, immunomodulators, antitumors, antibiotics).

Del Valle and Goodman [31] presented an efficient preparation of orthogonally protected *meso*-DAP based on ring-closing metathesis (RCM). The synthesis of protected *meso*-DAP **107** from compound **104** was shown in Scheme 14. Condensation of suitably protected L-allylglycine and D-vinyl-glycinol derivatives was followed by Grubbs' ring-closing metathesis to generate the key lactam intermediate **105**. The authors described two viable retrosynthetic routes synthesis. The cyclic olefins represent key lactone and lactam intermediates resulting from the RCM of linear ester and amide precursors, respectively. This

strategy features a Grubbs' ring-closing metathesis reaction as the key carbon-carbon bond-forming step and is complementary to recent reports utilizing asymmetric reduction or alkylation. For example Williams *et al.* [32] have investigated the use of RCM in the synthesis of differentially protected 2,7-diaminosuberic acid derivatives. The authors of the paper [31] described also synthesis of FK-565 **110** from lactam **105** (Scheme 15). Hydrolysis of lactam **105** and condensation with H-Ala-O*t*Bu provided the dipeptide alcohol **108**. Compound **108** was hydrogenated in the presence of 20% $Pd(OH)_2/C$ and then coupled with α-*tert*-butyl-(*N*-heptanoyl)-D-glutamate to give tripeptide alcohol **109**. Oxidation of **109** and treatment of the product with TFA/DCM afforded **110** (FK-565) in good yield.

The FK-565 **110** is synthetic analogue of FK-156 **111** (Scheme 16) isolated from *Streptomyces olivaceogriseus* [33,34]. Both FK-156 and FK-565 enhance host defense ability against microbial infections [35], exhibit strong antiviral activity [36] and remarkable antitumor potency [37-39]. In the literature there are described also other immunoactive peptides, e.g. RP 40639 **112** and RP 56142 **113** (Figure 4) incorporating the 2,6-DAP skeleton conjugated with lauric or palmitic acid [40].

In the synthesis of compounds FK-565 **110** and FK-156 **111** presented by myself the method described by Kołodziejczyk *et al.* [41] with small modification was used (Scheme 16). The compound **117** was used as substrate for synthesis of these peptides. Dibenzyloxycarbonyl-*meso*-diaminopimelic acid **114** was quantitatively converted with diazomethane into dimethyl ester or with *p*-nitrobenzyl alcohol into di-*p*-nitrobenzyl ester followed by selective hydrolysis at the L-center by means of protease from *Bacillus licheniformis* or α-chymotripsin. The next Z_2-*meso*-DAP-(D)-OMe ester or Z_2-*meso*-DAP-(D)-*O*-p-$BnNO_2$ **116** ester was converted into *N*-carboxyanhydride **117** in the reaction with PCl_5 or PBr_3 followed by acidic hydrolysis with 10 % AcOH in THF and Boc-protection of the amino group at the L-center to give selectively protected *meso*-DAP with free, ready for coupling carboxyl group at the L-center [42].

Aminolysis of the *N*-carboxyanhydride **117** with D-AlaONBn or GlyONBn was chosen to obtain the appropriate dipeptides with one free amino group as convenient intermediates for further peptides **111** (FK-156) and **110** (FK-565) synthesis. The BOP, DPPA or HBTU reagent, used for peptide bond formation, secured good yields and high chemical and chiral purity of the peptides.

Recently, Balducci *et al.* [43] reported an efficient enantioselective synthesis of both the enantiomers of the γ-methylene derivatives of 2,6-diaminopimelic acid.

Specific inhibitors of DAP enzymes are likely to be antimicrobial agents with low mammalian toxicity [44]. One of the enzymes in the DAP pathway is DAP epimerase, an unusual enzyme that interconverts LL-DAP and *meso*-DAP without the use of co-factors, metals, or reducible keto or imino functionality [44]. Diastereomeric mixture of oxa analogues of azi-DAP was found to irreversibly inhibit DAP epimerase, presumably due to thiol opening of the epoxide moiety [45]. Unfortunately, the crystal structures of the inactive disulfide form of DAP epimerase [46,47] do not allow reliable modeling of the substrate in the collapsed active site. Diaper *et al.* [48] described stereoselective synthesis of aziridine analogues of DAP **124**, **125** and **126** (Figure 5) and analysis of their interaction with DAP epimerase. Analogue LL-azi-DAP **125** selectively binds to Cys-73 of the enzyme active site where DL-azi-DAP **126** binds to Cys-217 via attack of sulfhydryl group on the methylene of the inhibitor aziridine ring. In conclusion, the authors wrote that the observed selectivity of azi-DAP inhibition is consistent with the two mechanism proposed for the epimerisation of LL-DAP and DL-DAP by DAP epimerase. More specifically that Cys-73 acts as a thiolate base to deprotonate LL-DAP, and Cys-217 does the same in the case of *meso*-DAP [49].

The biosynthesis of peptidoglycan (PGN) is a well-recognized target for antibiotic development [50,51]. For example, penicillins, cephalosporins, and vancomycin act by inhibiting key steps in the assembly of the PGN layers. PGN has also attracted considerable

attention as a ligand for receptors of the innate immune system of eukaryotes [44]. Chowdhury and Boons [44] described synthesis of DAP containing peptidoglycan fragments using metathesis cross coupling between properly protected allyl **127** and vinyl glycine derivatives **128** using Grubbs' second-generation catalyst followed by reduction of the double bond of the resulting compound e.g. **131** (Scheme 17). The DAP derivatives were used in the solution- and polymer-supported synthesis of biologically active PGN fragment structures **133**.

Nolen *et al.* [52] described synthesis of orthogonally protected (*S,S*)-diaminopimelic acid via a selective cross-metathesis between (*S*)-allyl glycine **134** and (*S*)-vinyl glycine **135** followed by hydrogenation (Scheme 18). By analogy, the authors prepared also (*S,S*)-diaminosuberic acid.

The principal biological role of *meso*-DAP consists in immunomodulation. The findings suggest that nucleotide-binding oligomerization domain NOD1 is a special sentinel molecule, especially in the epithelial barrier, allowing the intracellular detection of bacteria through recognizing *meso*-DAP or comparable moiety of peptidoglycans (PGN) from specified bacteria in cooperation with NOD2, thereby playing a key role in innate immunity [53]. Recently, Tada *et al.* [54] reported synergistic effect of NOD1 agonists (FK-565 and FK-156) and NOD2 agonist (muramyldipeptide, MDP) with toll-like receptor (TLR3, TLR4, and TLR9) agonists on human dendritic cells (DC) to generate IL-12, IFN-γ production and T helper type 1 cells.

In conclusion, an efficient enantioselective synthesis of diaminodicarboxylic acids, including 2,6-diaminopimelic acid (DAP) is very needed for searching of new immunostimulant and utilization of DAP derivatives in practice.

REFERENCES

1. Arakawa Y., Goto T., Kawase K. and Yoshifuji S., *Chem. Pharm. Bull.*, **43**, 535 (1995).

2. Sturn P.A. and Henry D.W., *J. Med. Chem*., **17**, 481 (1974).

3. Zeitler K. and Steglich W., *J. Org. Chem.,* **69**, 6134 (2004).

4. Cox R.J., *Nat. Prod. Rep*., **13**, 29 (1996).

5. Holcomb R.C., Schow S., Kaloustian S.A. and Powell D., *Tetrahedron Lett*., **35**, 7005 (1994).

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

7. Avenoza A., Cativiela C., Peregrina J.M. and Zurbano M.M., *Tetrahedron: Asymmetry*, **7**, 1555 (1996).

8. Tanaka K. and Sawanishi H., *Tetrahedron: Asymmetry*, **11**, 3837 (2000).

9. Hiebl J., Kollmann H., Rovenszky F. and Winkler K., *J. Org. Chem*., **64**, 1947 (1999).

10. Ferreira P.M.T., Maia H.L.S. and Monteiro L.S., *Tetrahedron Lett.,* **44**, 2137 (2003).

11. Jurgens A.R., *Tetrahedron Lett.,* **33**, 4727 (1992).

12. Bold G., Duthaler R.O. and Riediker M., *Angew. Chem. Int. Ed. Engl*., **28**, 497 (1989).

13. Gelb M.H., Lin Y., Pickard M.A., Song Y. and Vederas J.C., *J. Am. Chem. Soc.,* **112**, 4932 (1990).

14. Williams R.M., Im M.N. and Cao J., *J. Am. Chem. Soc.,* **113**, 6976 (1991).

15. Williams R.M. and Yuan C.G., *J. Org. Chem.,* **57**, 6519 (1992).

16. Williams R.M. and Yuan C.G., *J. Org. Chem.,* **59**, 6190 (1994).

17. Paradisi F., Porzi G. and Sandri S., *Tetrahedron: Asymmetry*, **12**, 3319 (2001).

18. Wang W., Xiong C.Y., Yang J.Q. and Hruby V.J., *Synthesis*, 94 (2002).

19. Collier P.N., Patel I. and Taylor R.J.K., *Tetrahedron Lett.,* **42**, 5953 (2001).

20. Collier P.N., Campbell A.D., Patel I. and Taylor R.J.K., *Tetrahedron*, **58**, 6117 (2002).

21. Sutherland A. and Vederas J.C., *Chem. Commun*., 224 (2002).

22. Gao Y., Lane-Bell P. and Vederas J.C., *J. Org. Chem.,* **63**, 2133 (1998).

23. Davis F.A. and Srirajan V., *J. Org. Chem.,* **65**, 3248 (2000).

24. Hernandez N. and Martin V.S., *J. Org. Chem.,* **66**, 4934 (2001).

25. Roberts J.L. and Chan C., *Tetrahedron Lett.,* **43**, 7679 (2002).

26. Sutherland A., Caplan J.F. and Vederas J.C., *Chem. Commun.,* 555 (1999).

27. Kubasch N. and Schmidt R.R., *Eur. J. Org. Chem.,* 2710 (2002).

28. Collier P.N., Campbell A.D., Patel I., Raynham T.M. and Taylor R.J.K., *J. Org. Chem.,* **67**, 1802 (2002).

29. Galeazzi R., Garavelli M., Grandi A., Monari M., Porzi G. and Sandri S., *Tetrahedron: Asymmetry*, **14**, 2639 (2003).

30. Bull S.D., Davies S.G., Parkin R.M. and Sanchez-Sancho F., *J. Chem. Soc. Perkin Trans. I.,* 2313 (1998).

31. Del Valle J.R. and Goodman M., *J. Org. Chem.,* **69**, 8946 (2004).

32. Williams R.M. and Liu J.W., *J. Org. Chem.,* **63**, 2130 (1998).

33. Gotoh T., Nakahara K., Nishiura T., Hashimoto S., Kino T. and Kuroda Y., *J. Antibiotics*, **35**, 1286 (1982).

34. Kawai Y., Nakamura K., Gotoh T., Uchida I., Tanaka H. and Imanaka H., *J. Antibiotics*, **35**, 1293 (1982).

35. Mine Y., Watanabe Y., Tawara S., Yokota Y., Nishida N., Goto S. and Kuwahara S., *J. Antibiotics*, **30**, 1059 (1983).

36. Okada S., Takeno H., Hemmi K., Kitaura Y. and Hashimoto M., *Chem. Pharm. Bull.,* **33**, 889 (1985).

37. Talmadge J.E., Lenz B., Schneider M., Phillips H. and Long C., *Cancer Immunol. Immunother*., **28**, 93 (1989).

38. Yi-Li W., Kaplan S., Whiteside T. and Herberman R.H., *Immunopharmacology*, **18**, 213

(1989).

39. Imamura N., Nakahara K., Kino T., Gotoh T., Kawamura I., Aoki H., Imanaka H. and Sone S., *J. Biol. Response Modif.,* **41**, 408 (1985).

40. Bouchaudon J., Dutruc-Rosset G., Farge D. and James C., *J. Chem. Soc. Perkin Trans. I.*, 695 (1989).

41. Kołodziejczyk A.M., Kołodziejczyk A.S. and Stoev S., *Int. J. Peptide Protein Res.*, **39**, 382 (1992).

42. Wodecki Z., Dzierzbicka K. and Kołodziejczyk A.M., (1995) XIII Polskie Sympozjum Peptydowe, Nadole, Poland, Peptydy 95, Abstract P7

43. Balducci D., Porzi G. and Sandri S., *Tetrahedron: Asymmetry*, **15**, 1085 (2004).

44. Chowdhury A.R. and Boons G.J., *Tetrahedron Lett.,* **46**, 1675 (2005).

45. Cox R.J., Durston J. and Roper D.I., *J. Chem. Soc. Perkin Trans. I.*, 1029 (2002).

46. Cirilli M., Zheng R.J., Scapin G. and Blanchard J.S., *Biochemistry*, **37**, 16452 (1998).

47. Lloyd A.J., Huyton T., Turkenburg J. and Roper D.I., *Acta Crystallogr D60*, 397 (2004).

48. Diaper C.M., Sutherland A., Pillai B., James M.N.G., Semchuk P., Blanchard J.S. and Vederas J.C., *Org. Biomol. Chem.,* **3**, 4402 (2005).

49. Koo C.W., Sutherland A., Vederas J.C. and Blanchard J.S., *J. Am. Chem. Soc.,* **122**, 6122 (2000).

50. Koch A.L., *Clin. Microbiol. Rev.,* **16**, 673 (2003).

51. Weidenmaier C., Kristian S.A. and Peschel A., *Curr. Drug Targets*, **4**, 643 (2003).

52. Nolen E.G., Fedorka C.J. and Blicher B., *Synthetic Comm.,* **36**, 1707 (2006).

53. Uehara A., Fujimoto Y., Kawasaki A., Kusumoto S., Fukase K. and Takada H., *J. Immunol.,* **177**, 1796 (2006).

54. Tada H., Aiba S., Shibata K.I., Ohteki T. and Takada H., *Infect. Immun.,* **73**, 7967 (2005).

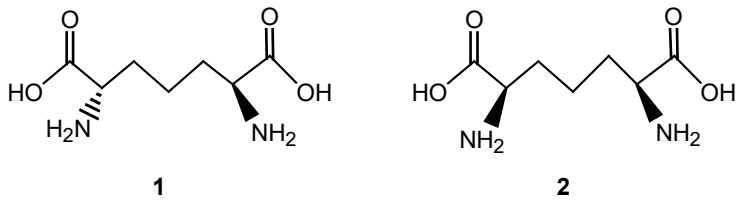
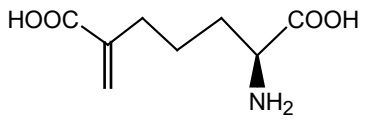
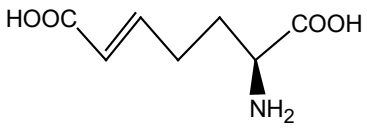


Figure 1. (2*S*,6*S*)-Diaminopimelic acid (DAP) **1** and *meso*-(2*S*,6*R*)-diaminopimelic acid (*meso*-DAP) **2**.



57



58

Figure 2. Nonproteinogenic amino acids **57** and **58** [26].

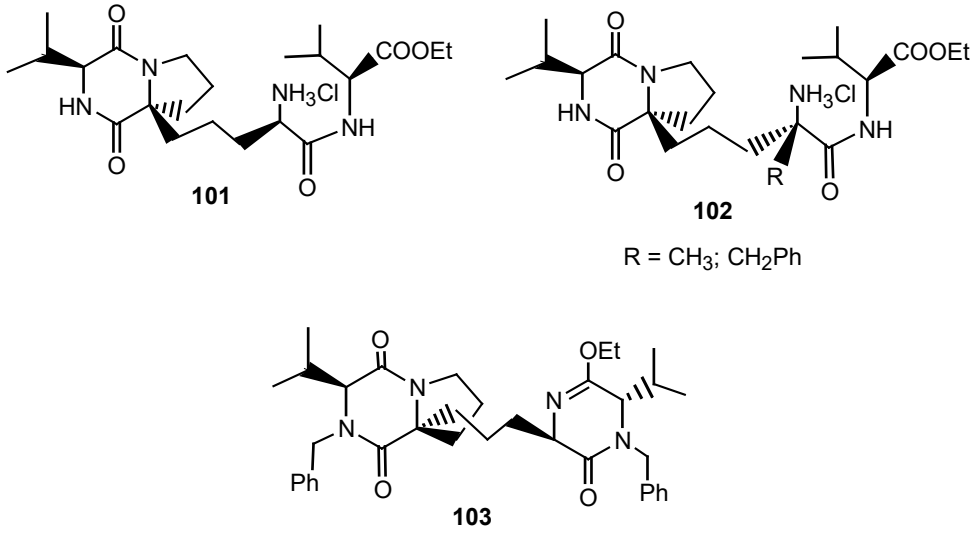
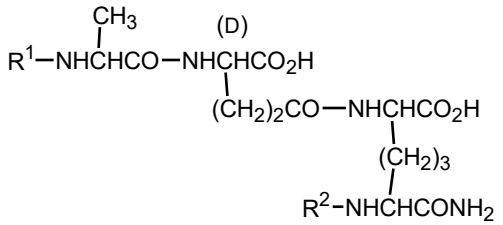


Figure 3. Peptides containing the 2,6-diaminopimelic acid [29].



112 (RP 40639) R^1 = $CH_3(CH_2)_{10}CO$; R^2 = NH_2CH_2CO; DAP: rac.
113 (RP 56142) R^1 = $CH_3(CH_2)_{10}CO$; R^2 = H; DAP: L

Figure 4. Immunoactive peptides RP 40639 **112** and RP 56142 **113** [40].

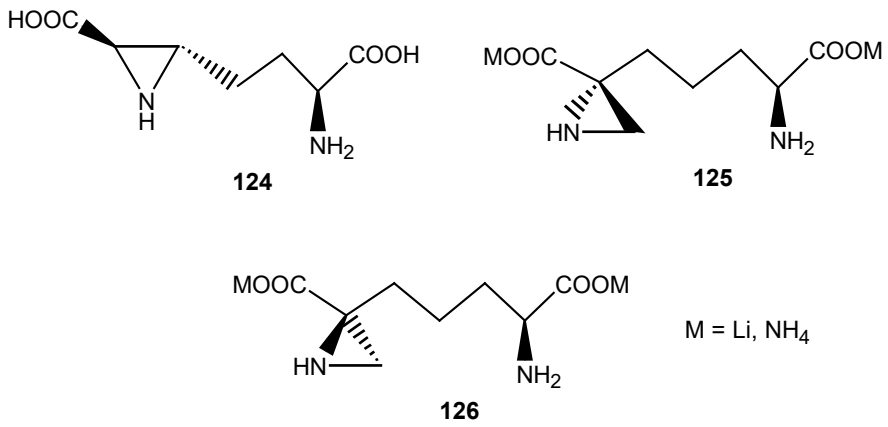
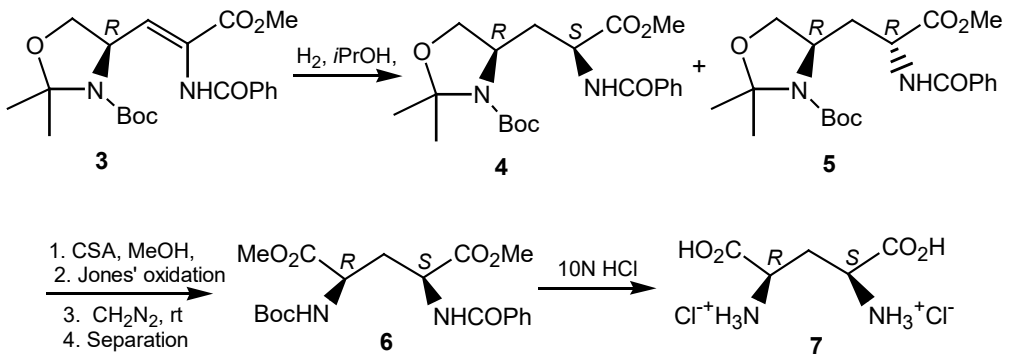
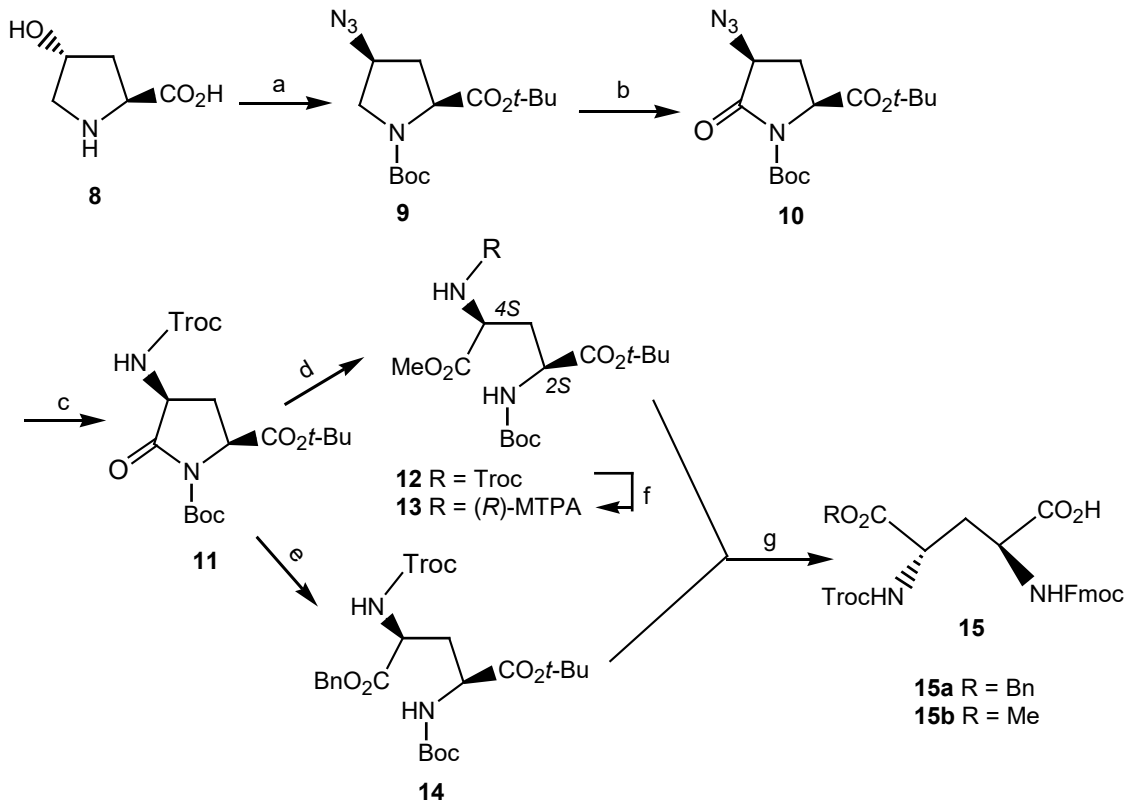


Figure 5. Aziridine analogues of DAP [48].

Scheme 1. Synthesis of *meso*-2,4-diaminoglutaric acid [7].

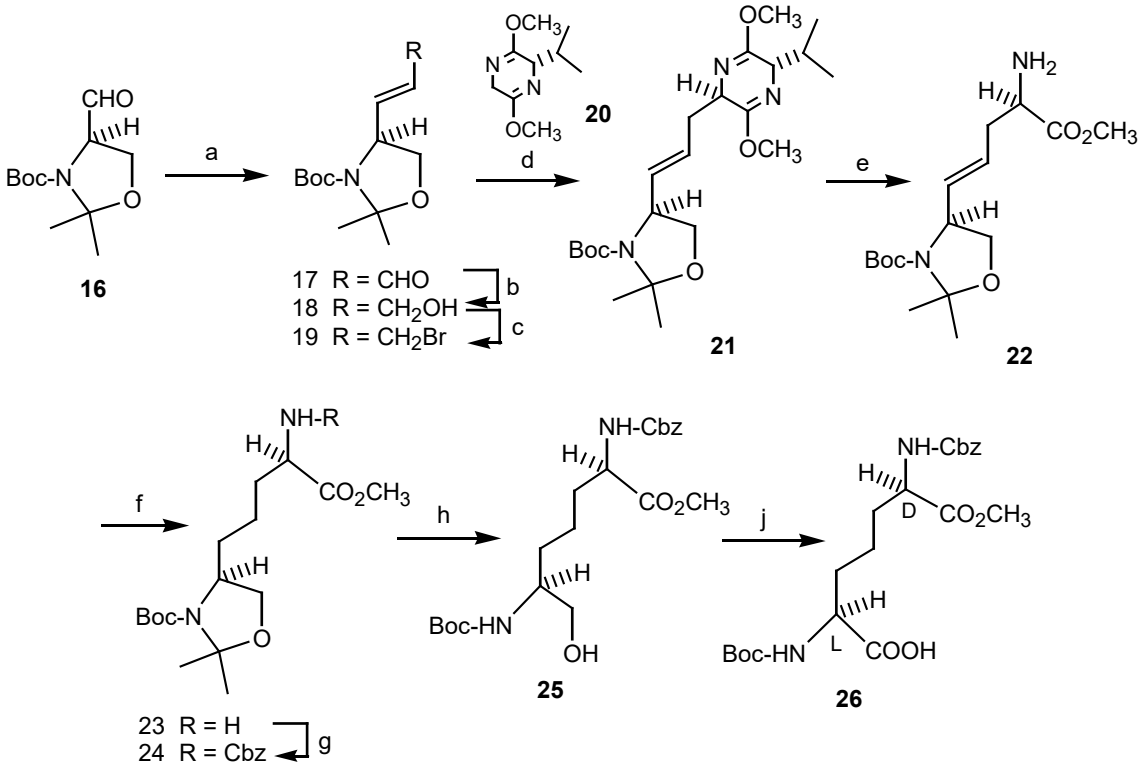


Scheme 2. Stereospecific synthesis of differentially protected (2*S*,4*S*)-2,4-diaminoglutaric acid [8].



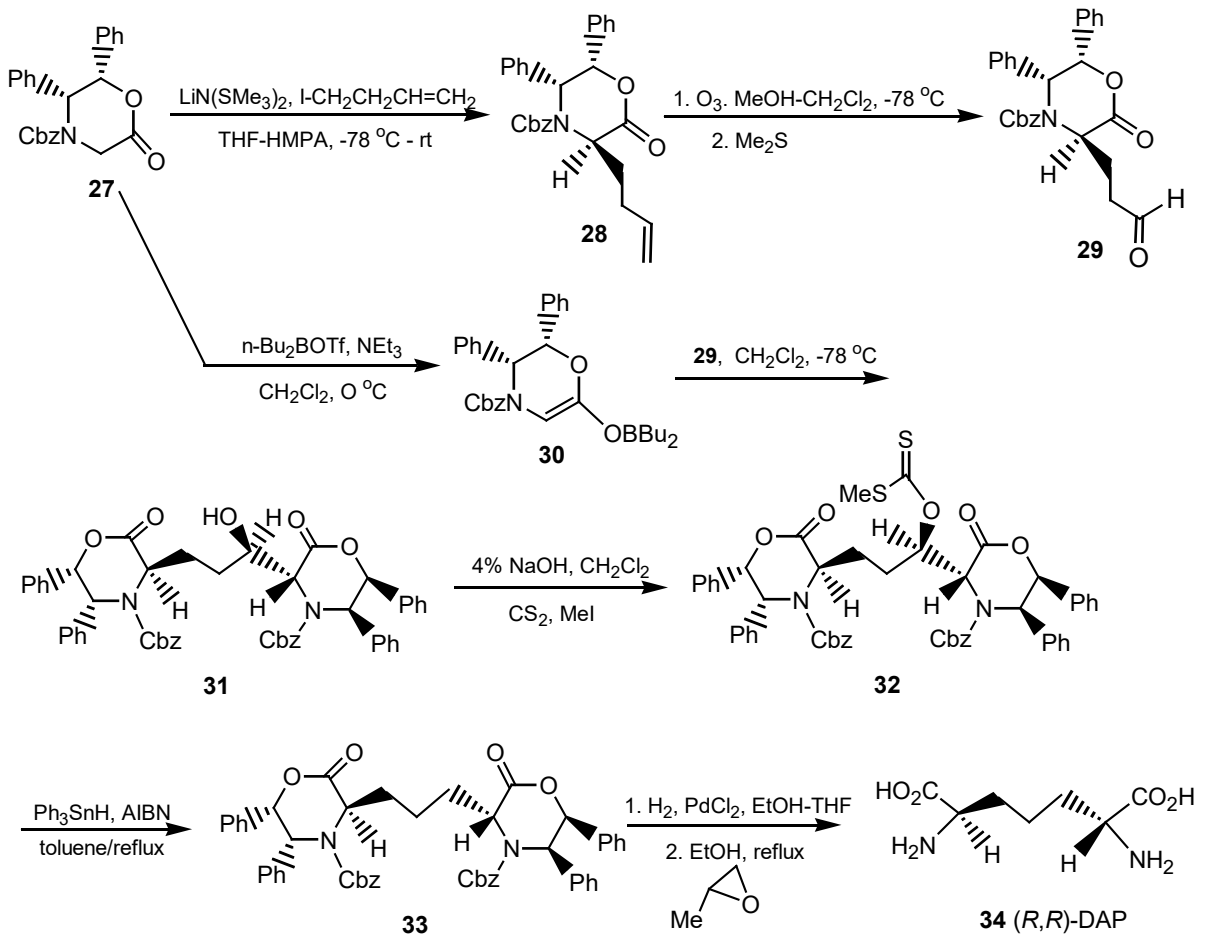
a: Boc_2O, Et_3N; *O-tert*-butyl-*N*,*N*-diisopropylisourea, THF; MsCl, pyridine; NaN_3, DMF, 70^0C; b: RuO_2xH_2O, 10% aq.$NaIO_4$/AcOEt; c: 10% Pd-C/H_2, MeOH; Troc-Cl, Et_3N, CH_2Cl_2; d: 1M LiOH/THF, rt; CH_2N_2, MeOH; e: 1M LiOH/THF, rt; BnBr, NaI, K_2CO_3, DMF, rt; f: zinc dust, AcOH, rt; (*R*)-MTPA-Cl, 4-DMAP, THF; g: TFA, CH_2Cl_2, rt; Fmoc-Cl, Na_2CO_3, H_2O/THF, O^oC.

Scheme 3. Stereoselective synthesis of differentially protected *meso*-DAP [11].

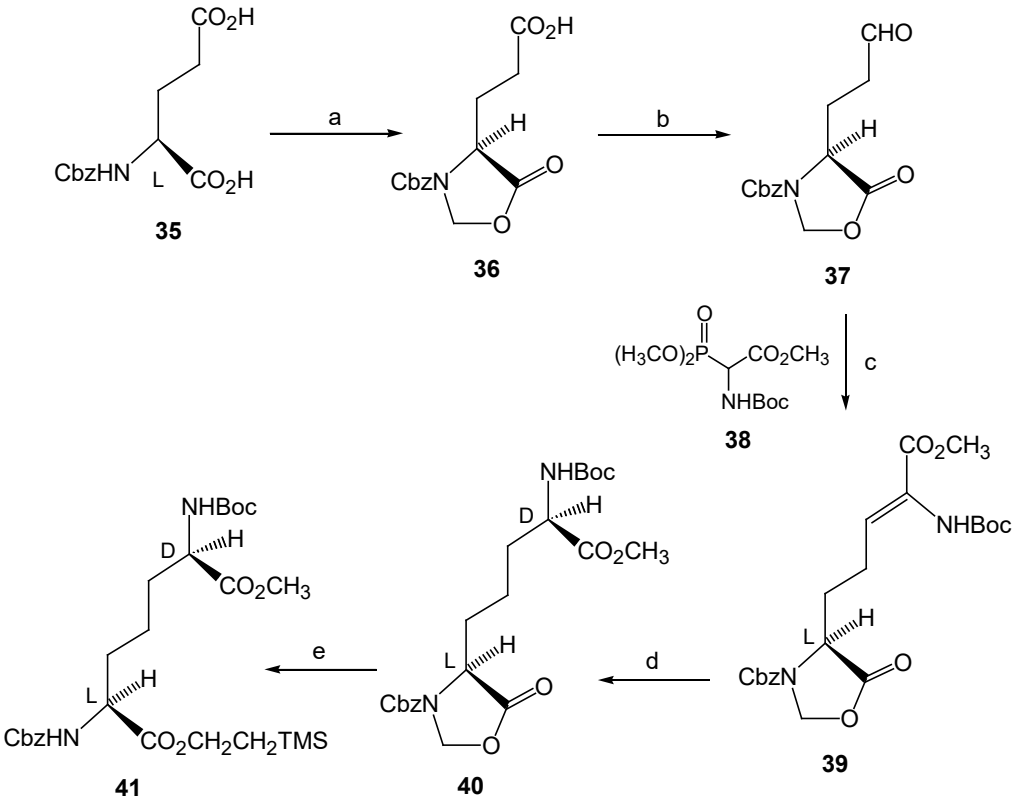


a: Ph_3P=CHCHO, toluene, Δ; b: DIBAL, CH_2Cl_2, O^oC; c: Ph_3P, CBr_4, CH_2Cl_2, O^oC; d: *n*-BuLi, THF, -78^oC;
e: 0.1N HCl, THF, H_2O; f: H_2/Pd/C, EtOAc; g: Cbz-Cl, Et_2O, $NaHCO_3$; h: *p*-TsOH, H_2O, CH_3OH; j: PDC, DMF

Scheme 4. Asymmetric synthesis of (*R*,*R*)-DAP **34** [15].

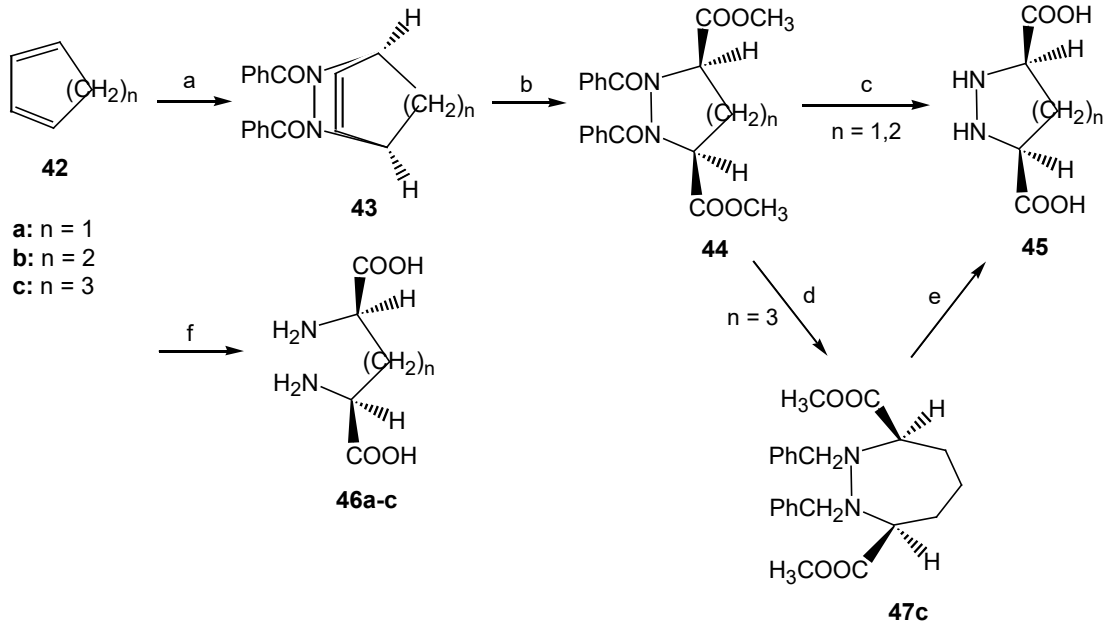


Scheme 5. Synthesis of differentially protected *meso*-DAP **41** [5].



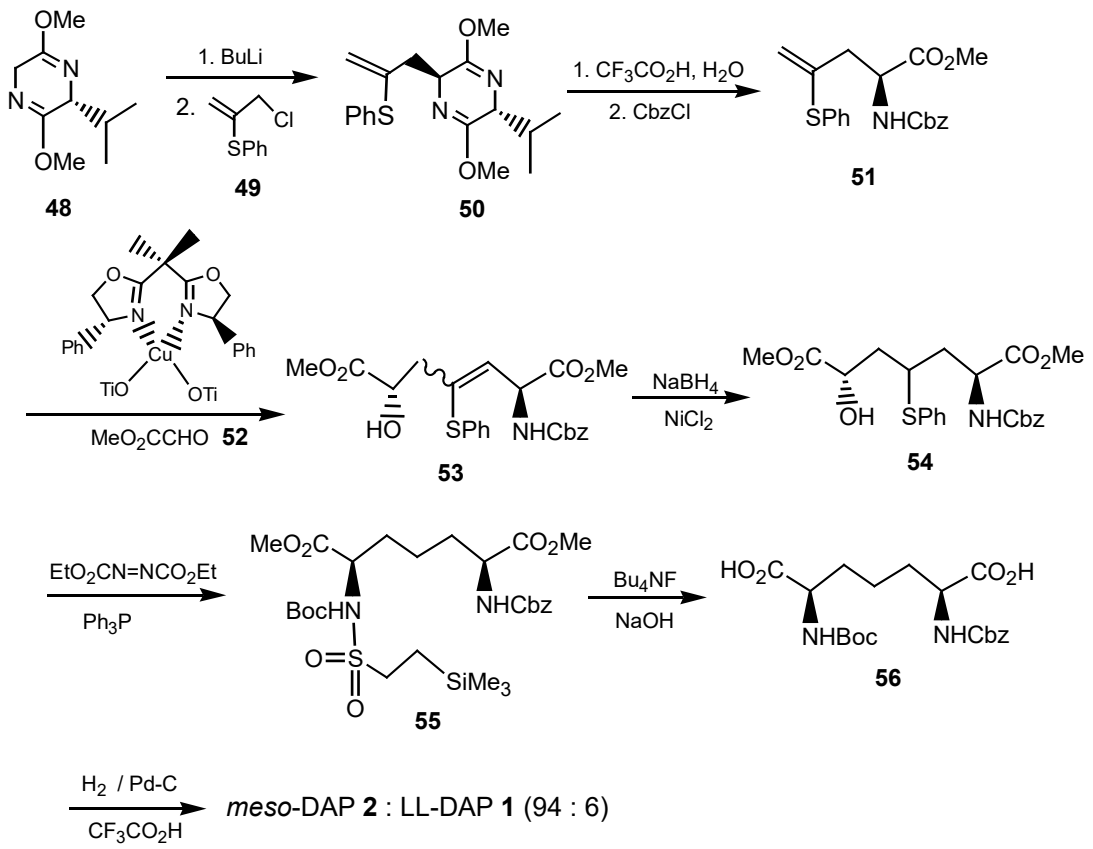
a: $(CH_2O)_n$, toluene, Δ; b: BH_3SMe_2; PCC; c: KHMDS; d: H_2 (40 psi) $[Rh(NBD)_2]ClO_4$ (*S*,*S*)-chiraphos (3:1 D:L); e: $TMSCH_2CH_2OH$, LiHMDS
NBD - norbornadiene

Scheme 6. Stereospecific synthesis of *meso*-diaminodicarboxylic acids [1].

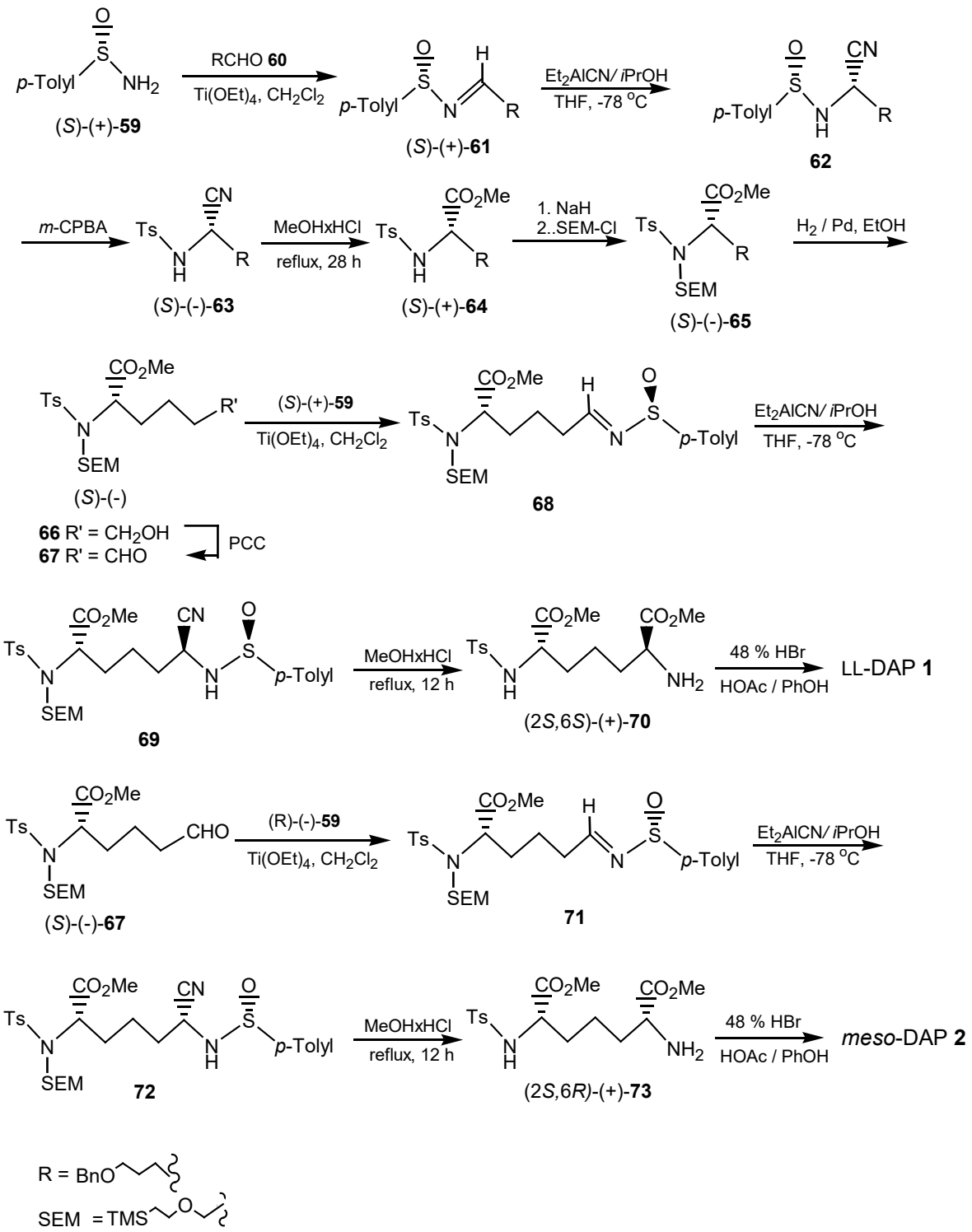


a: $(PhCON)_2$, CCl_4; b: RuO_2 (cat.), aq $NaIO_4$AcOEt, 0^oC, then CH_2N_2 or $SOCl_2$/MeOH; c: 6N HCl-AcOH
d: $BH_3.(CH_3)S$, THF; e: 20%$Pd(OH)_2$/C, H_2, 2N HCl-AcOH, 4 atm, then 2N HCl, 50^oC; f: PtO_2, H_2, 2N HCl, 4 atm

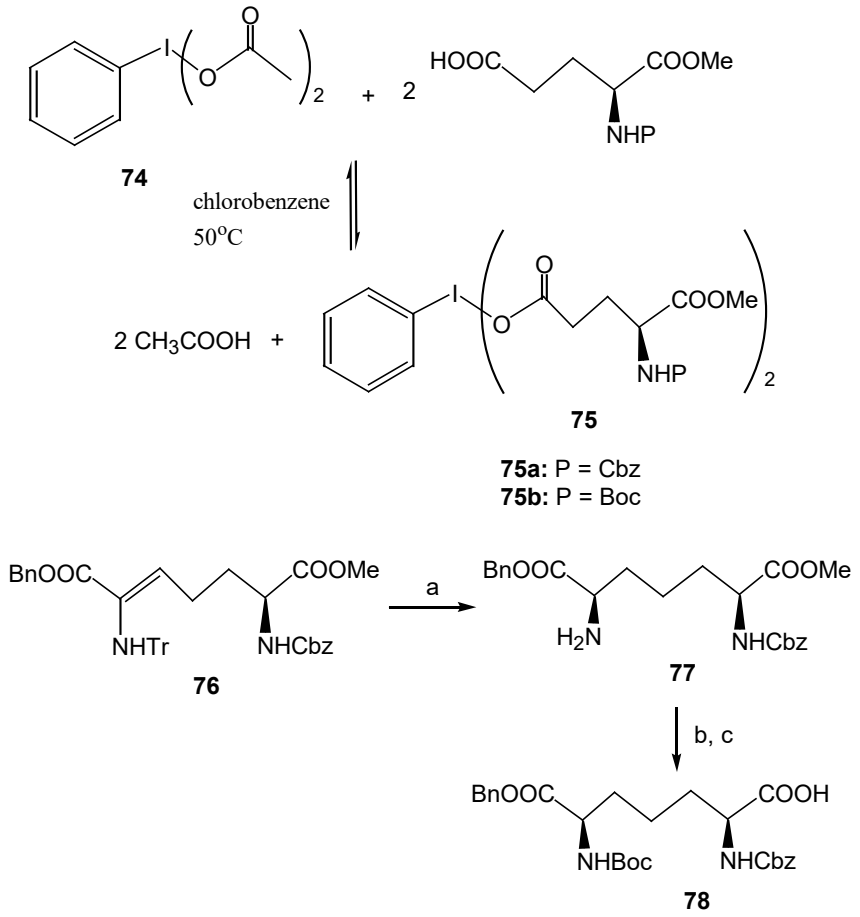
Scheme 7. Stereoselective synthesis of *meso*-DAP [22].



Scheme 8. Asymmetric synthesis of LL-DAP and *meso*-DAP [23].

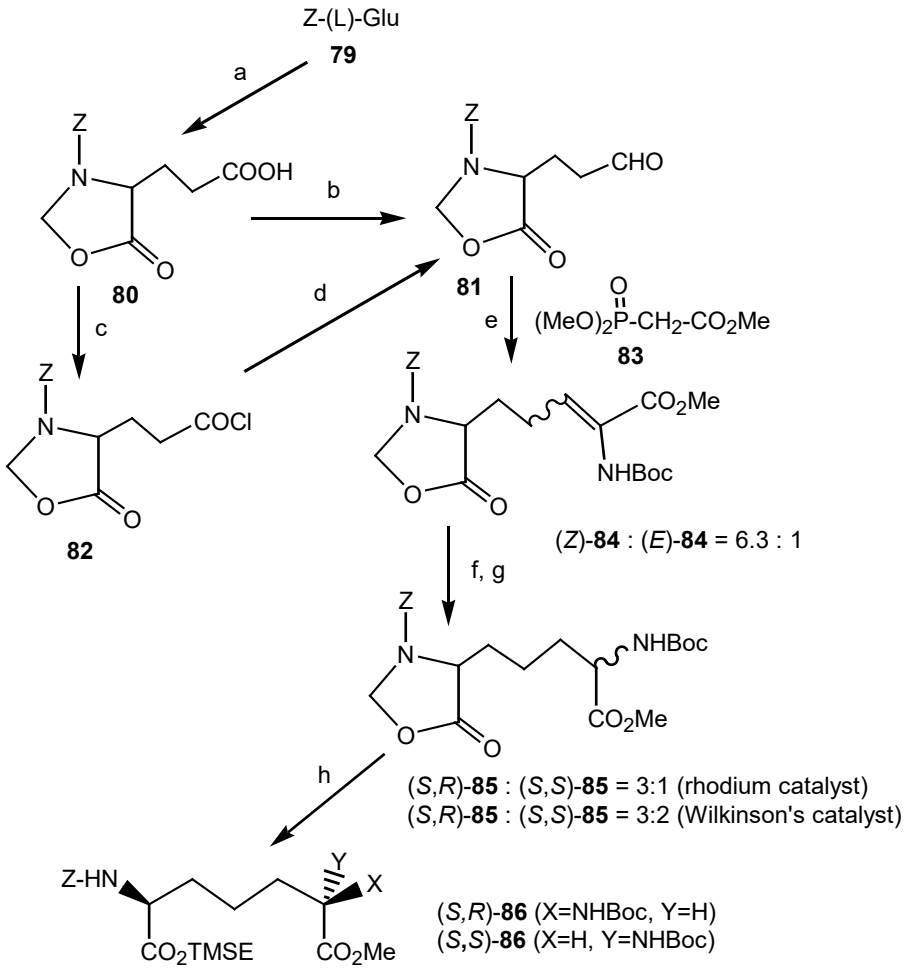


Scheme 9. Synthesis of diaminopimelic acid analogues [21].



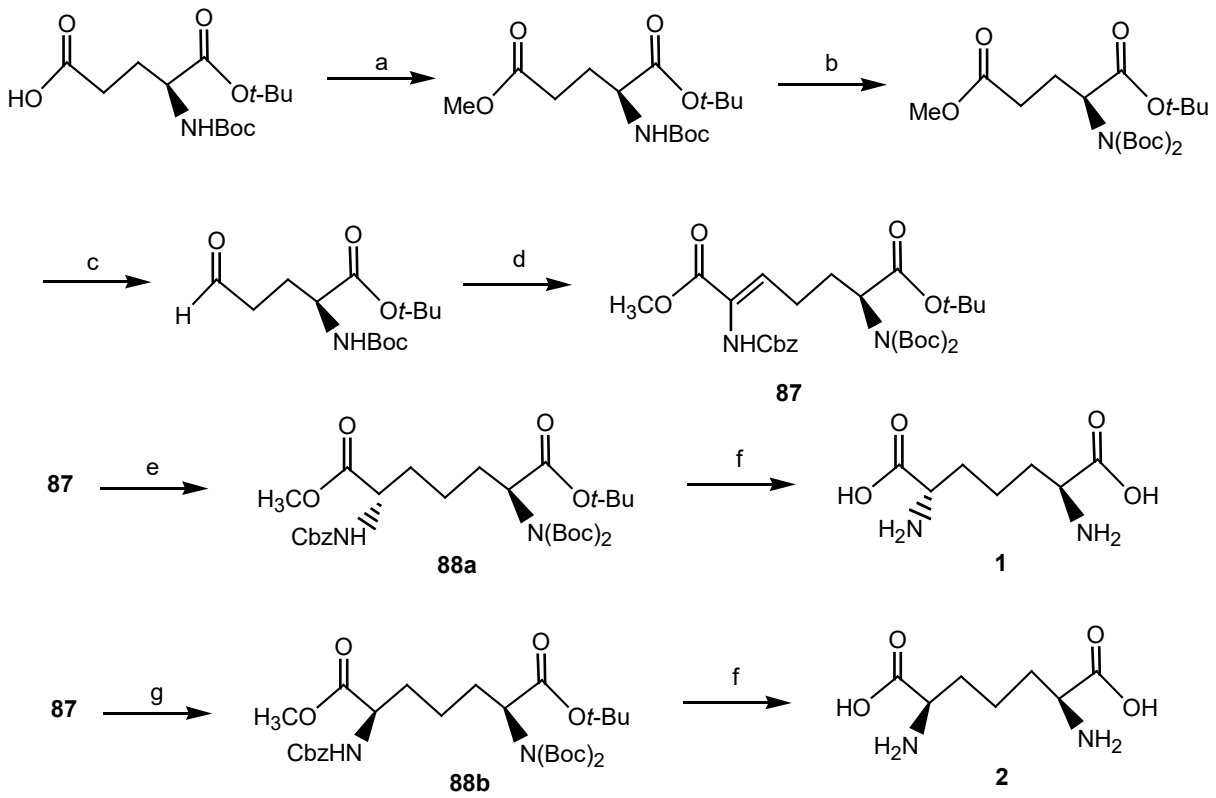
a. [(COD)Rh((*R*,*R*)-Et-DuPHOS)]BF_4, MeOH, 100 ps, H_2; b: Boc_2O, NEt_3, DMAP, CH_2Cl_2; c: LiOH, MeOH, H_2O

Scheme 10. Synthesis of *meso*-diaminopimelic acid derivatives [27].



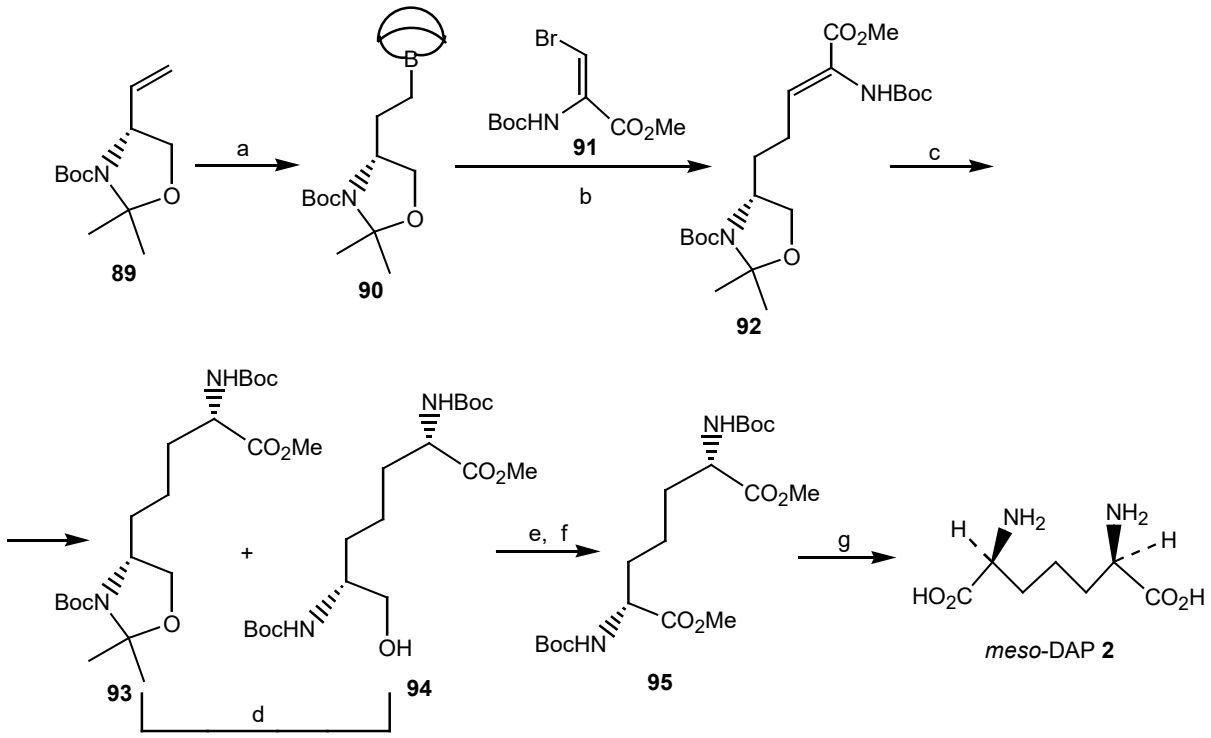
a: $(CH_2O)_n$, toluene, heat (86%); b**:** BH_3SMe_2, 0^oC - room temp.; periodinane Dess-Martina, room temp. (53%); c**:** $SOCl_2$, heat (76%); d**:** $LiAl(OtBu)_3H$, THF, -78^oC (73%); e**:** KHMDS, THF, -78^oC- -30^oC [88%, (*Z*)-**84** : (*E*)-**84** = 6.3 : 1]; f**:** $Me_3Si-CH_2-CH_2OH$, LiHMDS, THF, 0^oC (65%); g**:** $[RhCl(PPh_3)_3]$, H_2, MeOH [90%, (*S*,*R*)-**85** : (*S*,*S*)-**85** = 3 : 2]; h**:** TMSE-OH, LiHMDS, THF, 0^oC [70%, (*S*,*R*)-**86** : (*S*,*S*)-**86** = 3 : 2]

Scheme 11. Synthesis of (2*S*,6*S*)- and *meso*-DAP via asymmetric hydrogenation [18].



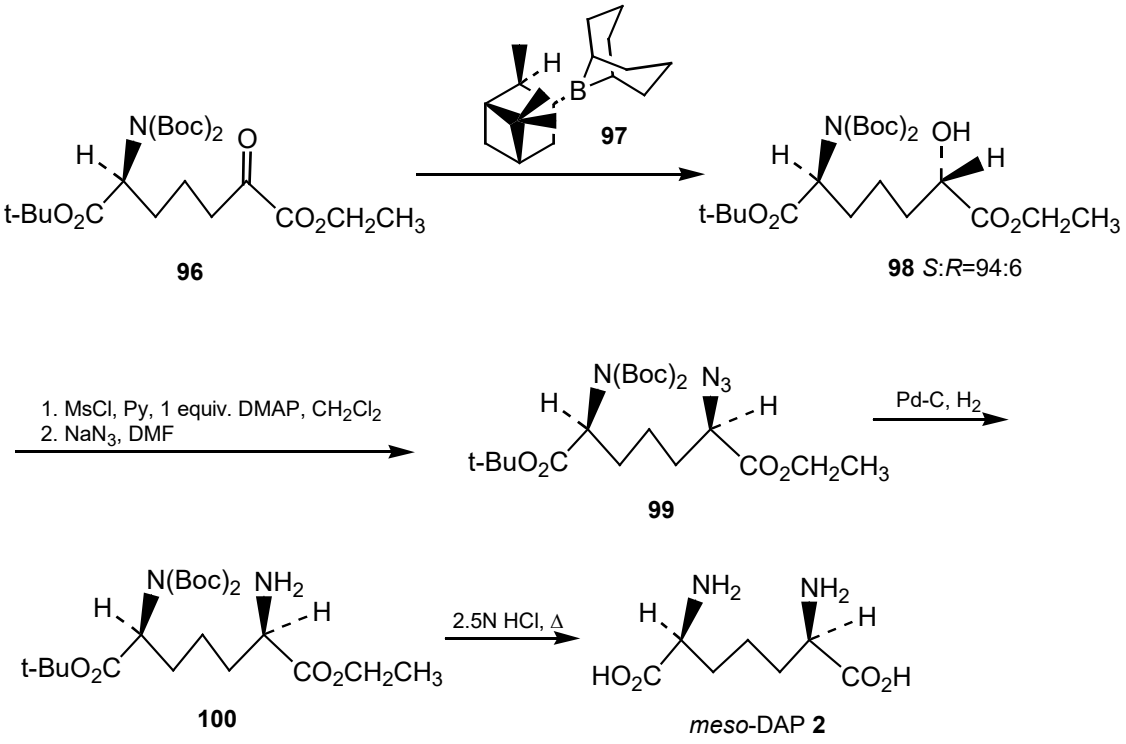
a. MeOH, DCC, DMAP, TEA, CH_2Cl_2; b. $(Boc)_2O$, DMAP, CH_3CN; c. DIBAL, ether, -78^oC;
d. $(MeO)_2P(O)CH(NHCbz)COOMe$, DBU, CH_2Cl_2, r.t.; e. [Rh(I)(COD)(*S*,*S*)-Et-DuPHOS][OTf], H_2(70 psi), MeOH, 24h; f. 30% HBr/PhOH, HOAc; g. Rh(I)(COD)(*R*,*R*)-Et-DuPHOS][OTf], H_2(70 psi), MeOH, 24h.

Scheme 12. Stereoselective synthesis of *meso*-DAP [19].



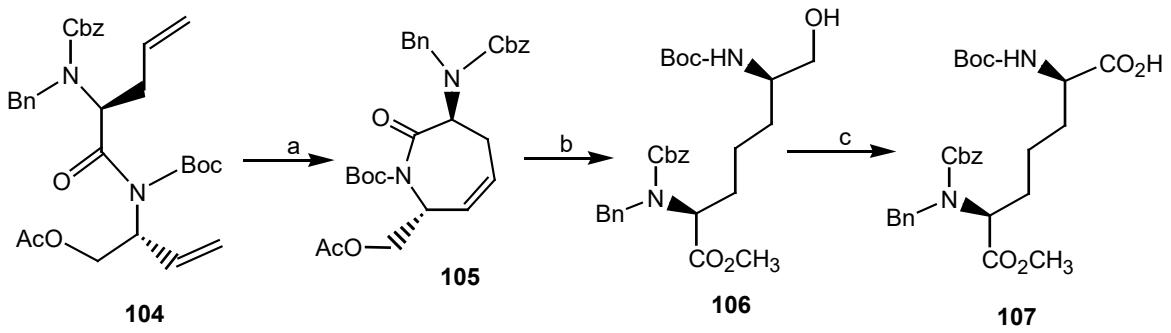
a: 9-BBN, THF; b: $PdCl_2$ $CHCl_3$, 3M K_3PO_4, THF-DMF; c: 250 psi H_2, [(COD)Rh(*S*,*S*)-Et-DuPHOS)]OTf, toluene, 60°C; d: TFA, MeOH, 0°C; e: Jones' reagent, acetone; f: $TMSCHN_2$, MeOH-toluene; g: 5M HCl, 70°C; propyleneoxide, EtOH.

Scheme 13. Asymmetric synthesis of differentially protected *meso*-DAP [25] .



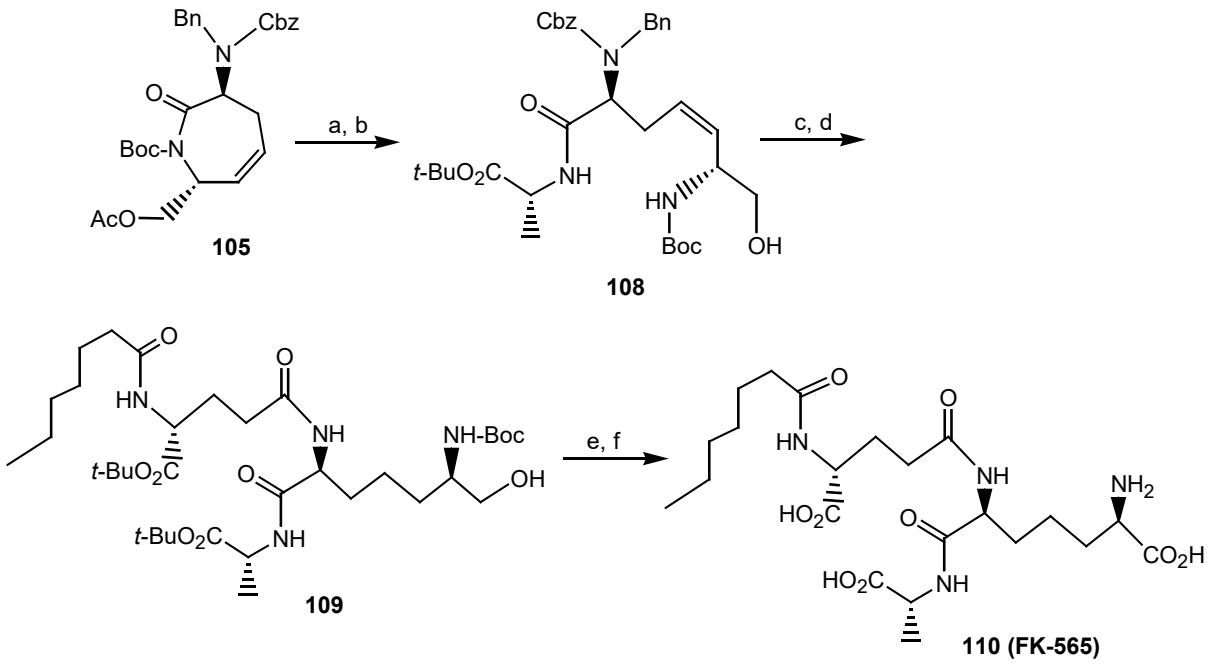
R-(+)-Alpine-Borane **97**, made in situ from *R*-(+)-α-pinene and 9-BBN

Scheme 14. Synthesis of orthogonally protected DAP derivatives [31].



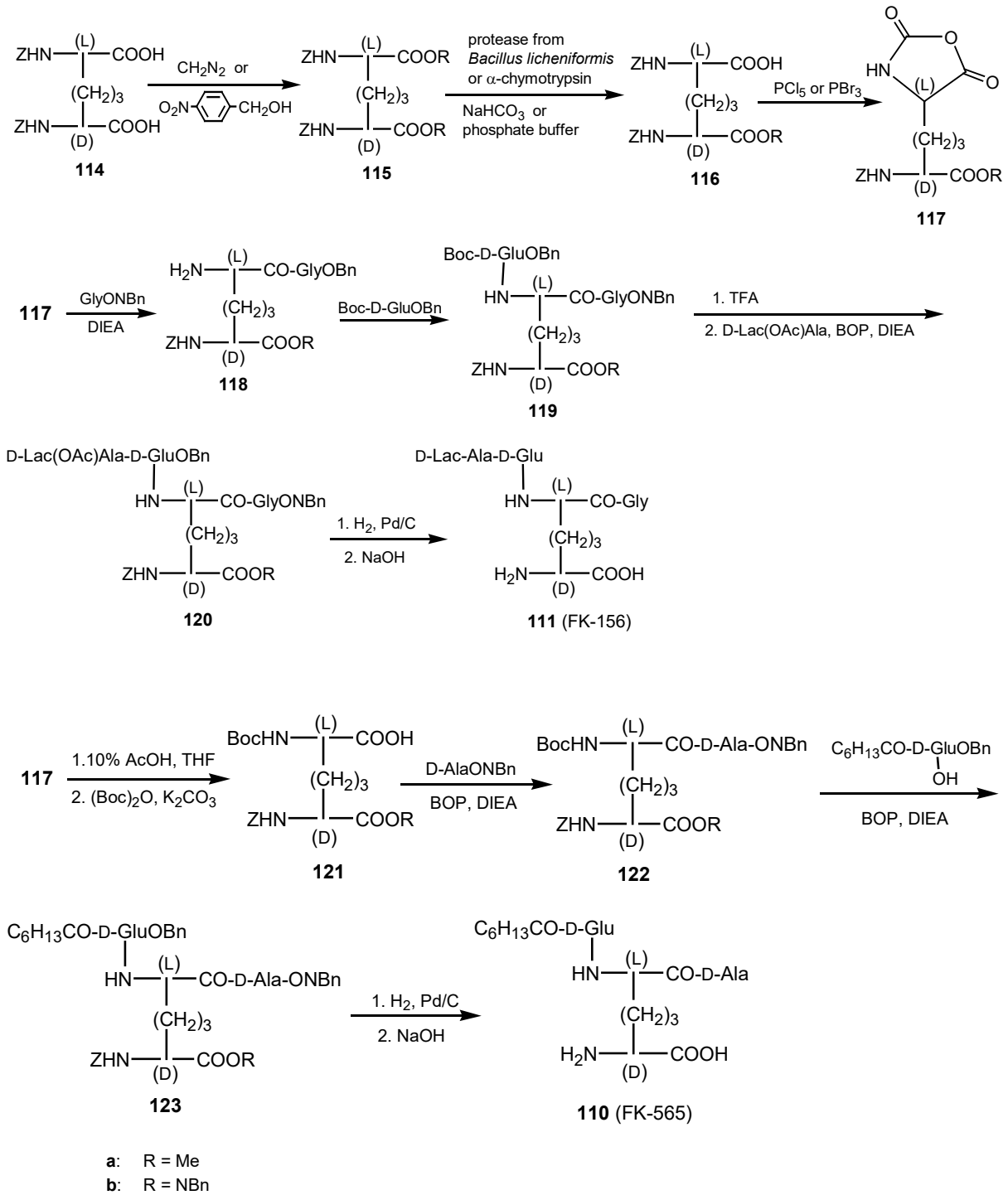
a: 2 mol % Grubbs' second-generation catalyst, DCM, reflux; 2M aq LiOH, THF; b: MeI, K_2CO_3, DMF; 2 mol % $[Ir(COD)PyPCy_3]PF_6$, H_2, DCM; c: NaClO, $NaClO_2$, TEMPO, $MeCN/H_2O$

Scheme 15. Synthesis of FK-565 from lactam **105** [31].

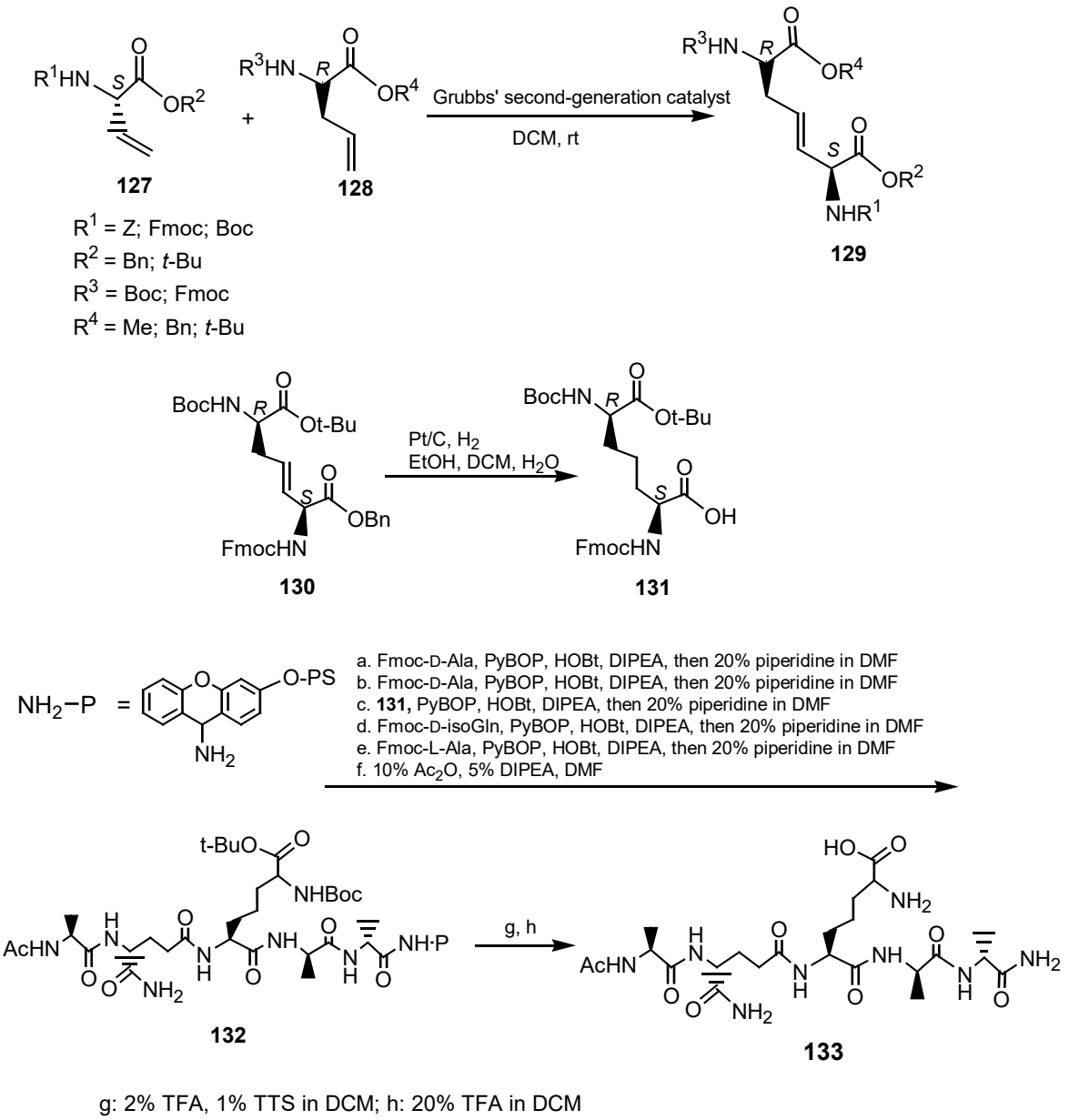


a: 2 M aq LiOH, THF; b: D-Ala-O*t*-Bu, DEPBT, TEA, DCM; c: 20% $Pd(OH)_2/C$, H_2, MeOH;
d: α-*tert*-butyl-(*N*-heptanoyl)-D-glutamate, PyBOP, TEA, DCM; e: NaClO, $NaClO_2$, TEMPO, $MeCN/H_2O$;
f: 95% TFA/DCM

Scheme 16. Synthesis of FK-156 and FK-565 [41].

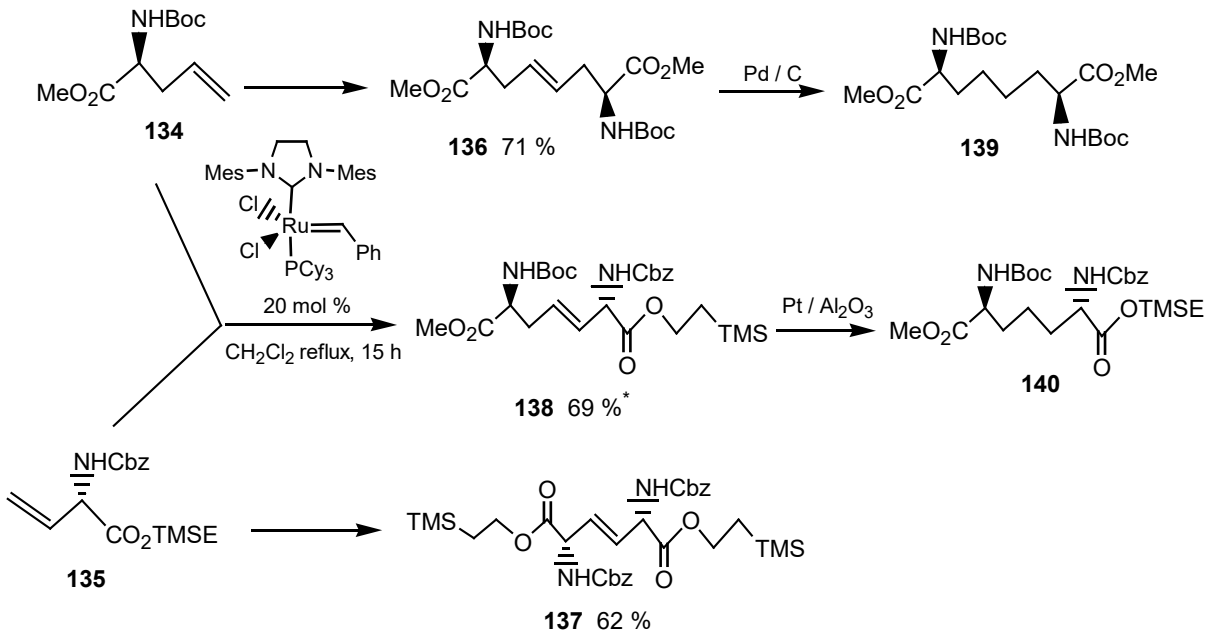


Scheme 17. Polymer-supported synthesis of DAP containing peptide derivatives from Gram-negative PGN [44].



g: 2% TFA, 1% TTS in DCM; h: 20% TFA in DCM

Scheme 18. Synthesis of orthogonally protected (2*S*,6*S*)-DAP via olefin cross-metathesis [52].



*E/Z ratio 8:1 based on integration of Me-ester