Amino Acids (2003) 24:231–243
DOI 10.1007/s00726-002-0403-8

Amino
Acids
Printed in Austria

Synthesis and use of *N*,*N*-di-Boc-glutamate γ-semialdehydes and related aldehydes

Review Article

V. Constantinou-Kokotou and **V. Magrioti**

Chemical Laboratories, Agricultural University of Athens, Athens, Greece

Received April 24, 2002
Accepted August 13, 2002
Published online January 30, 2003;

Summary. This review article focuses on the synthesis and reactions of *N*,*N*-di-Boc glutamate and aspartate semialdehydes as well as related aldehydes. These building blocks are prepared according to various strategies from glutamic and aspartic acids and find interesting synthetic applications. In the first part, the methods for the synthesis of *N*,*N*-di-Boc-amino aldehydes are summarized. The applications of these chiral synthons for the synthesis of unnatural amino acids and other bioactive compounds are discussed in the second section.

Keywords: Amino aldehydes – Chiral synthons – *N*,*N*-di-Boc-Glutamate semialdehydes – Wittig reaction – Unnatural amino acids

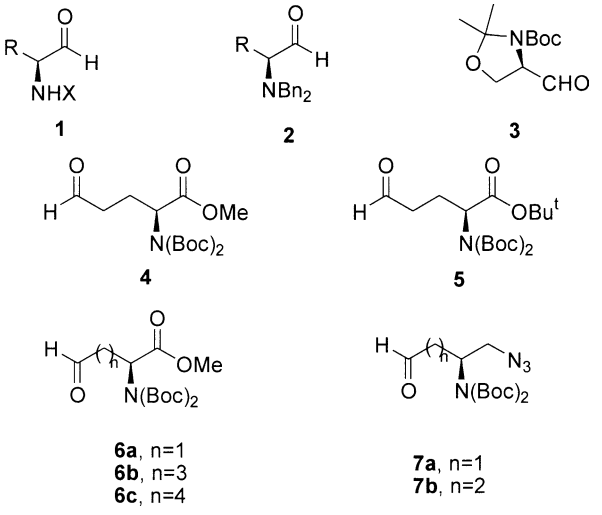
Abbreviations: AcNH-TEMPO, 4-acetamido-2,2,6,6-tetramethyl-1-piperidinyloxy free radical; AIBN, 2,2′-azobis(2-methylpropionitrile); Aliquat, methyltrioctylammonium chloride; Bn, benzyl; Boc, *tert*-butoxycarbonyl; Bu^t, *tert*-butyl; *m*-CPBA, 3-chloroperoxybenzoic acid; DAST, diethylaminosulfur trifluoride; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; (*R*,*R*)-(+)-DET, (*R*,*R*)-(+)-diethyltartrate; DIBALH, diisobutyl aluminium hydride; DMAP, 4-dimethylaminopyridine; DMF, dimethylformamide; Et_3N, triethylamine; KHMDS, potassium bis(trimethylsilyl)amide; (*S*)-LLB, lanthanium-lithium-bis-metallic binaphthol catalyst; MsCl, methanesulfonyl chloride; NEM, *N*-ethylmorpholine; NMO, 4-methylmorpholine N-oxide; PPA, propylphosphonic acid anhydride; TBHP, *tert*-butyl hydroperoxide; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TMSI, 1-(trimethylsilyl)imidazole; Trt, trityl.

Introduction

α-Amino acids have been employed for a long time by organic chemists as chiral building blocks in synthetic organic chemistry. Early examples describe the use of natural L-amino acids. However, today the chiral pool of amino acids includes D-enantiomers and a variety of enantiomerically pure amino acids not occurring in nature. According to one strategy a specific α-amino acid is incorporated into a natural product or a biologically active compound. The second strategy involves the transformation of α-amino acids into different classes of compounds, such as amino alcohols and amino aldehydes. *N*-Protected α-amino aldehydes (**1**) have been prepared by various methods and have found several applications (Jurczak and Golebiowski, 1989). However, *N*-protected α-amino aldehydes are easily racemized and their careful handling is needed. *N*,*N*-Dibenzylamino aldehydes (**2**) have been proven particular useful into C-C bond forming processes (Reetz, 1999). The presence of two protective benzyl groups is of crucial importance in influencing the direction and degree of diastereoselectivity (Reetz, 1991). Another synthetically important development concerns 1,1-dimethylethyl 4-formyl-2,2-dimethyl-oxazolidine-3-carboxylate (**3**), known as Garner's aldehyde. This aldehyde is prepared in almost enantiomerically pure form (ee 95%) in four steps from serine (Garner and Park, 1992) and has been extensively used in asymmetric synthesis till todate (Liang et al., 2001). *N*-Monoprotected glutamate and aspartate semialdehydes have been reported and found application in the synthesis of unnatural amino acids (Gosselin and Lubell, 1998, Meffre, 1999).

This review article focuses on the synthesis and reactions of *N,N*-di-Boc-glutamate (**4**, **5**) and aspartate

semialdehydes (**6a**) as well as related aldehydes (**6b**,**c**, **7a**,**b**). These building blocks have been prepared from glutamic and aspartic acid and have already found interesting synthetic applications.



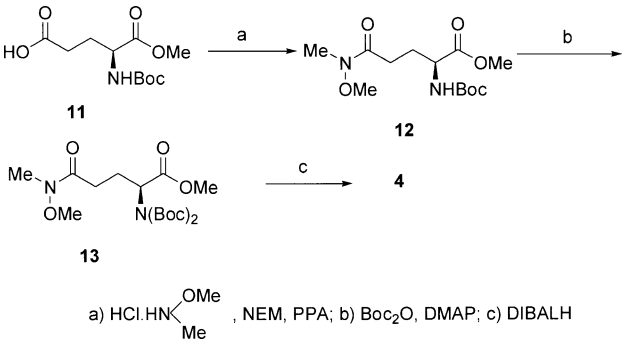
Scheme 1

1. Synthesis of optically active N,N-di-Boc-amino aldehydes

In the first part of this article, the methods for the synthesis of *N*,*N*-di-Boc-amino aldehydes are summarized.

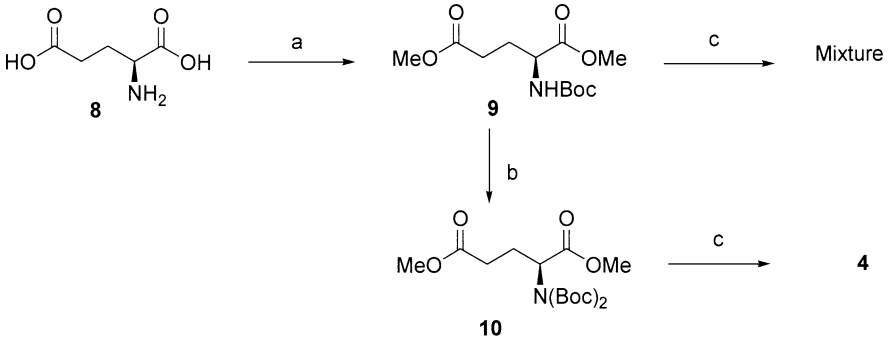
The method for the synthesis of methyl (2*S*)-2-[bis(*tert*-butoxycarbonylamino)]-5-oxopentanoate (**4**) developed by Kokotos and Martin groups is outlined in Scheme 2 (Kokotos et al., 1998a). Both carboxyl groups of Glu (**8**) were converted into methyl esters and the amino group was subsequently protected by two Boc groups. Selective reduction of γ-methyl ester with DIBALH produced aldehyde **4** in high overall yield (79%). The introduction of the second *N*-Boc group minimizes the nucleophilic power of the nitrogen atom and its presence is critical, as reduction of *N*-monoprotected derivative leads to a mixture of products. Methyl (2*S*)-2-[bis(*tert*-butoxycarbonylamino)]-4-oxobutanoate (**6a**) was synthesized by similar reactions starting from Asp (Padron et al., 1998).

Kessler et al. synthesized aldehyde **4** as outlined in Scheme 3. Methyl Boc- glutamate **11** was transformed into the Weinreb amide **12** by using *N,O*-dimethylhydroxylamine hydrochloride, *N*-ethylmorpholine (NEM) and propylphosphoric acid anhydride (PPA) as coupling reagent. A second Boc group was introduced and the resulting Weinreb amide was transformed into aldehyde **4** by reduction with DIBALH with an overall yield of 57% (Burkhart et al., 1997).

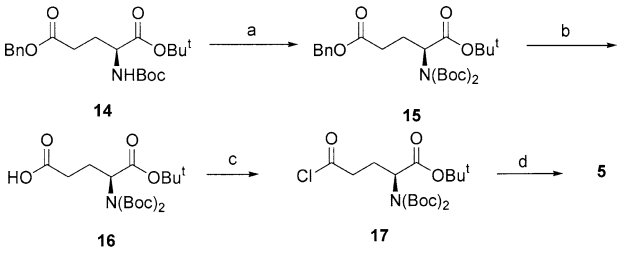


Scheme 3

The method proposed by Kokotos et al., which is based on the regioselective reduction of dimethyl glutamate, seems advantageous as compared to that proposed by Kessler et al., because differentiation of the two carboxylic groups of the starting Glu is not needed.

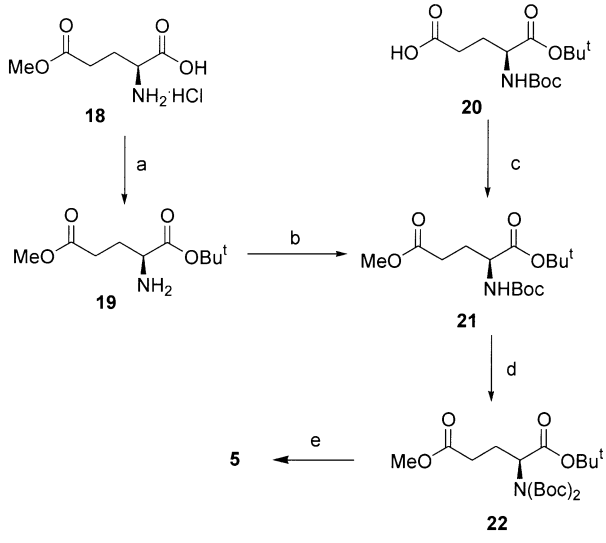


Scheme 2



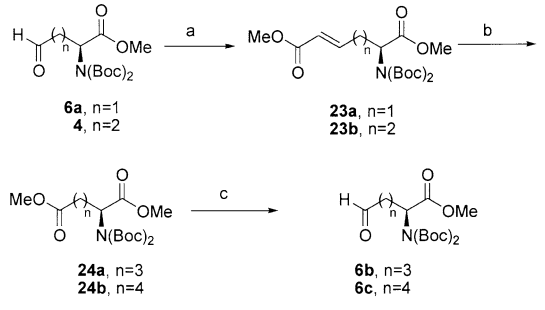
a) Boc_2O, DMAP, Et_3N, CH_2Cl_2; b) H_2, 5% Pd/C, EtOH; c) $Me_2NC(Cl)=C(CH_3)_2$, CH_2Cl_2; d) H_2, 5% Pd/C, 2,6-lutidine, THF

Scheme 4



a) $CH_2=C(CH_3)_2$, H_2SO_4, dioxane; b) Boc_2O, Et_3N, MeOH; c) $ClCO_2Me$, DMAP, Et_3N, CH_2Cl_2; d) Boc_2O, DMAP, MeCN; e) DIBALH, Et_2O, -78°C

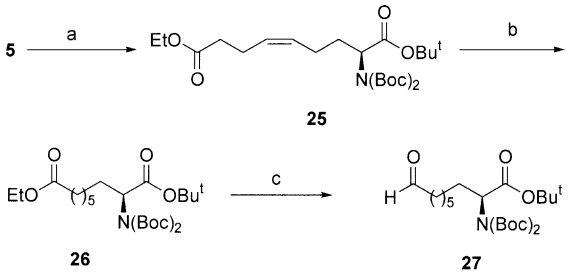
Scheme 5



a) $PH_3P=CHCOOMe$, C_6H_6, 0°C; b) H_2, 10% Pd/C, EtOAc; c) DIBALH, Et_2O, -78°C

Scheme 6

tert-Butyl (2*S*)-2-[bis(*tert*-butoxycarbonylamino)]-5-oxopentanoate (**5**) was synthesized starting from benzyl *α-tert*-butyl Boc-glutamate (**14**) (Scheme 4). After introduction of a second Boc group, the benzyl group was removed. The γ-carboxyl group was converted into acyl chloride and subsequently into aldehyde **5** via Rosemmund reaction in overall yield of 56% (Bold et al., 1990).



a) $EtOOC(CH_2)_3\overset{\oplus}{P}Ph_3\overset{\ominus}{Br}$, KHMDS, THF, -78 °C; b) H_2, 10% Pd/C, MeOH; c) DIBALH, Et_2O, -78 °C

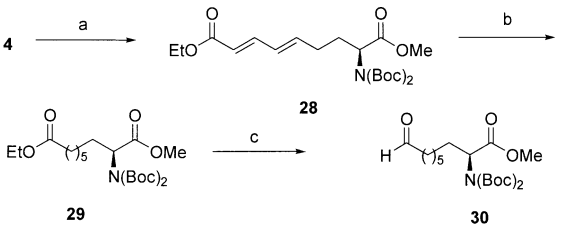
Scheme 7

The second synthesis of aldehyde **5** is based on the selective reduction of γ-methyl ester group of **22** using DIBALH (Scheme 5). The di-Boc derivative **22** was prepared starting either from γ-methyl glutamate (**18**) (Constantinou-Kokotou et al., 2001) or from *α-tert*-butyl glutamate (**20**) (Adamczyk et al., 1999a).

Higher carbon homologs of *N*,*N*-di-Boc-amino aldehydes were prepared as described in Scheme 6. Aldehydes **4** and **6a** were submitted to Wittig reaction using methyl (triphenylphosphoranylide)acetate to obtain the corresponding *E*-unsaturated esters **23a**,**b**. Catalytic hydrogenation followed by selective reduction of the ω-methyl ester group produced aldehydes **6b** and **6c** in overall yield 69% and 72%, respectively (Padron et al., 1998).

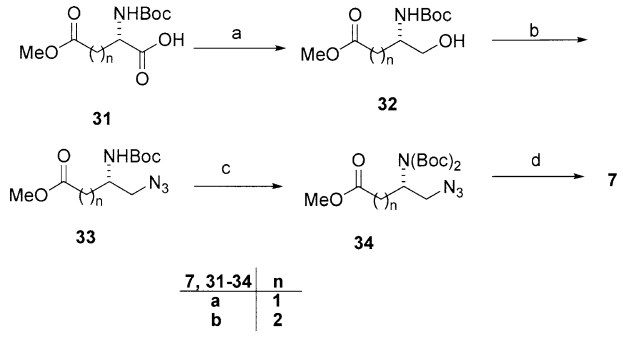
Wittig reaction of the aldehyde **5** with the ylide, generated from [3-(ethoxycarbonyl)propyl] triphenylphosphonium bromide and KHMDS, in THF at −78°C, yielded the *Z*-olefin **25** (Scheme 7). The corresponding hydrogenated compound **26** was reduced under controlled conditions by DIBALH to afford *tert*-butyl (2*S*)-2-[bis(*tert*-butoxycarbonyl) amino]-9-oxononanoate (**27**, yield 19%), indicating that an ethyl ester group located at the end of the long chain is selectively converted into aldehyde, while the *α-tert*-butyl ester remains unaffected (Constantinou-Kokotou et al., 2001).

The Horner-Wadsworth-Emmons olefination reaction of aldehyde **4** with the phosphonate anion generated from triethyl-4-phosphonocrotonate by treatment with LiOH afforded compound **28** (Scheme 8). After hydrogenation of **28**, compound **29**



a) $EtOOCCH{=}CHCH_2P(=O)(OEt)_2$,$LiOH{\cdot}H_2O$, mol. sieves, THF; b) H_2, 10% Pd/C, MeOH; c) DIBALH, Et_2O, -78 °C

Scheme 8



a) i. $ClCO_2Et$, N-methylmorpholine, THF, -10°C; ii. $NaBH_4$, MeOH, 0°C to rt; b) i. MsCl, Et_3N, CH_2Cl_2, 0°C to rt, ii. NaN_3, DMF, 55 °C; c) Boc_2O, DMAP, MeCN, 55°C; d) i. DIBALH, Et_2O, -78°C

Scheme 9

was reduced under controlled conditions by DIBALH at −78°C to afford aldehyde **30** in overal yield 41% (Magrioti and Constantinou-Kokotou, 2002).

γ-Methyl esters of *N*-Boc protected Asp **31a** and Glu **31b** were converted into alcohols **32** (Scheme 9) by reduction of their corresponding mixed anhydrides with $NaBH_4$ (Kokotos 1990). The hydroxy group of **32** was activated by the conversion to mesylate and replaced by the azido group (Kokotos and Constantinou-Kokotou, 1992). A second Boc group was introduced by treatment of **33** with $(Boc)_2O$ in the presence of DMAP. Treatment of amino alcohol **32** with $(Boc)_2O$ in the presence of DMAP produced *N*,*O*-di-Boc derivative of the amino alcohol, indicating that the second *N*-Boc group must be introduced after conversion of the hydroxy group to the azide group. Reduction of the methyl ester group of compounds **34** using DIBALH under controlled conditions produced aldehydes **7** (overall yield 40%) (Markidis and Kokotos, 2001).

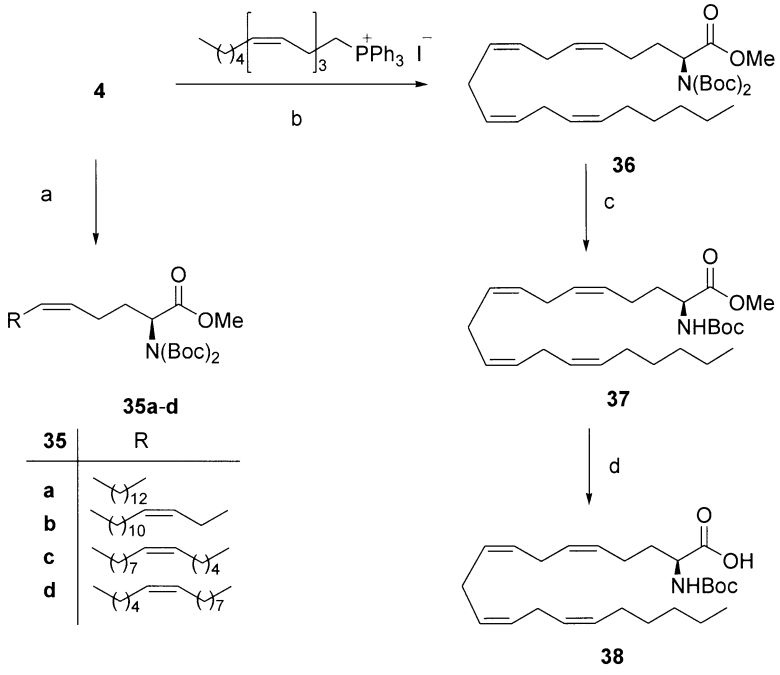
2. Synthetic applications of N,N-di-Boc-glutamate semialdehydes

Aldehydes **4** and **5**, as polyfunctional chiral compounds, are interesting chiral synthons for the preparation of biologically active molecules. In the second part of this article, the applications of these aldehydes for the synthesis of unnatural amino acids and other bioactive compounds are summarized.

The lipidic α-amino acids (LAAs) are a class of unnatural amino acids with long aliphatic side chains, combining structural features of amino acids with those of fatty acids (Kokotos et al., 1996b; Constantinou-Kokotou and Kokotos, 1999). Amides and esters of LAAs, as well as lipopeptides, show interesting biological properties (Kokotos et al., 1996a; Nicolaou et al., 1997). A general approach to enantioselective synthesis of saturated LAAs is based on the oxidative cleavage of amino diols obtained by the regioselective opening of enantiomerically enriched 2,3-epoxy alcohols (Kokotos et al., 1996c). However, this method has limitations and may be used only for saturated derivatives. The use of *N*,*N*-di-Boc amino aldehydes permits the synthesis of various unsaturated amino acids, including 2-amino-arachidonic acid and 2-amino-oleic acid. Wittig reaction of aldehyde **4** with the suitable saturated or unsaturated ylides produced δ,ε-unsaturated amino acids and 2-amino-arachidonic acid (Scheme 10) (Kokotos et al., 1998a; Padron et al., 1998).

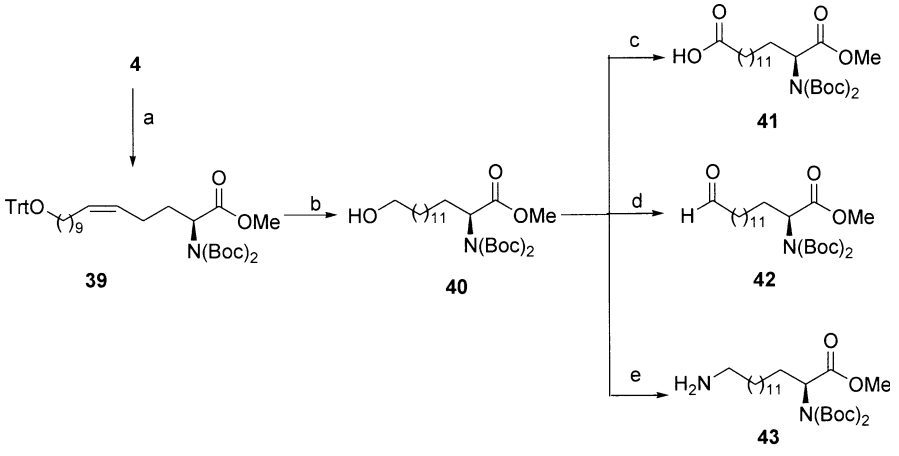
It should be noted that 2-amino alcohols and 1,2-diamines obtained from such amino acids exhibited interesting cytotoxic acitivity (Kokotos et al., 1998b, Markidis et al., 2001). Furthermore, enantiopure and racemic long chain 2-amino alcohols and diamines have been reported to possess several biological activities. For example (*R*)-2-aminohexadecanol displays immunosuppresant activity (Hirose et al., 1996) comparable to the potent immunosuppresant FTY270 (Adachi et al., 1995). Racemic 2-amino alcohols and diamines were found to inhibit human platalet phospholipase A_2 (Noula et al., 1996) and cytosolic and secretory phospholipases A_2 (Lucas et al., 2000). Moreover, racemic 2-amino-hexadecanol and 1,2-hexadecanediamine inhibit the carrageenin-induced paw edema in rats (Kokotos et al., 1999) and present Leismanicidal activity (Del Olmo et al., 2002).

Most recently, the synthesis of enantiopure ω-functionalized C15 α-amino carboxylates has been reported (Markidis and Kokotos, 2002). Aldehyde **4**



a) $RCH_2PPh_3^+I^-$, KHMDS, $C_6H_5CH_3$, -78°C, b) KHMDS, $C_6H_5CH_3$, -78°C; c) i. HCl, THF, ii. Boc_2O, Et_3N, MeOH; d) NaOH, dioxane

Scheme 10

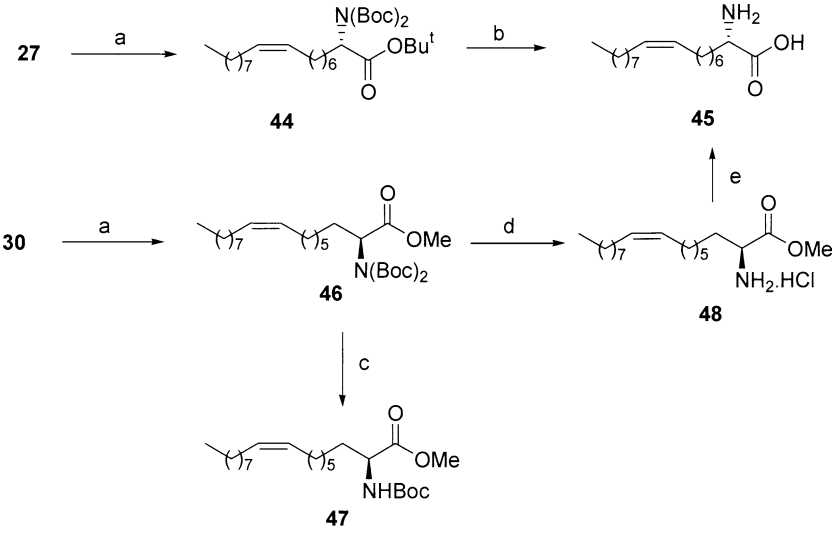


a) $TrtO(CH_2)_{10}PPh_3^+I^-$, KHMDS, toluene; b) H_2, 10% Pd/C, MeOH; c) NaOCl, AcNH-TEMPO, Aliquat, KBr, $NaHCO_3$, CH_2Cl_2, H_2O; d) NaOCl, AcNH-TEMPO, NaBr, $NaHCO_3$, EtOAc, toluene, H_2O; e) i) MsCl, Et_3N, CH_2Cl_2, ii) NaN_3, DMF, iii) H_2, 10% Pd/C, MeOH.

Scheme 11

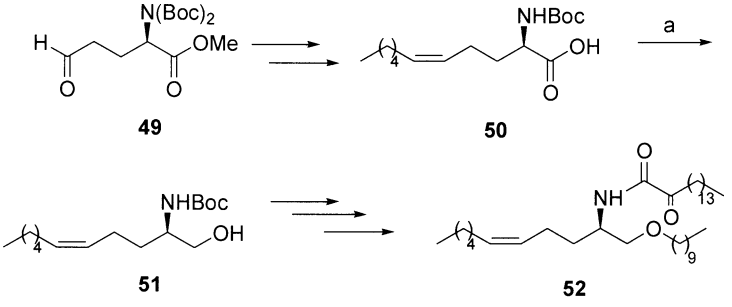
reacted with the ylide generated by treatment of $TrtO(CH_2)_{10}PPh_3^+I^-$ with KHMDS at 0°C. Catalytic hydrogenation of compound **39** gave the saturated methyl ester of ω-hydroxy α-amino acid **40**, which was converted into ω-carboxy, ω-oxo, and ω-amino derivatives **41**–**43** (Scheme 11).

Racemic α-amino-oleic acid is used as a tissue treatment for advanced generation bioprostheses (Chen et al., 1994). Two methods for the synthesis of enantiopure (*S*)-2-amino-oleic acid (**45**) have been presented. The first one is based on the Wittig reaction of aldehyde **27** with the ylide generated from *n*-nonanyl-triphenylphosphonium bromide and deprotection under acidic conditions (Constantinou-Kokotou et al., 2001) (Scheme 12). The second one is based on the Wittig reaction of aldehyde **30** with the



a) $C_9H_{19}PPh_3^+Br^-$, KHMDS, toluene, -78 °C; b) 50%TFA/CH_2Cl_2, neutralization; c) $Mg(ClO_4)_2$, MeCN; d) 4N HCl/Et_2O; e) 1N NaOH, MeOH.

Scheme 12



a) i. cyanuric fluoride, C_5H_5N, ii. $NaBH_4$, MeOH

Scheme 13

same ylide and deprotection of Boc group followed by saponification (Scheme 12) (Magrioti and Constantinou-Kokotou, 2002). One out of the two Boc groups may be selectively removed by treatment with $Mg(ClO_4)_2$. Most recently two new methods for such selective removal of one Boc group have appeared (Yadav et al., 2002a, 2002b).

Aldehyde **7** has been used as synthon for the synthesis of chiral terminal 1,2-diamines through a Wittig olefination reaction with various stabilized or non-stabilized ylides (Markidis and Kokotos, 2001).

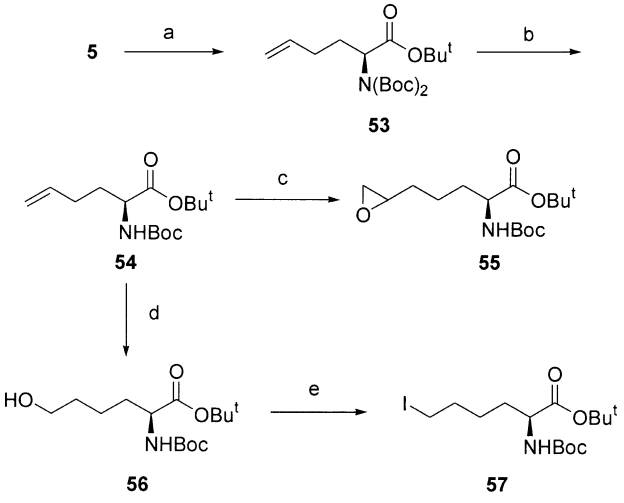
All the unnatural amino acids presented in the above mentioned syntheses, using *N*,*N*-di-Boc-glutamate semialdehydes as starting material, are optically pure (>95%) (Kokotos et al., 1998a; Padron et al., 1998; Constantinou-Kokotou et al., 2001; Magrioti and Constantinou-Kokotou, 2002; Markidis and Kokotos, 2002).

Methyl (2*R*)-2-[bis(*tert*-butoxycarbonylamino)]-5-oxopentanoate (**49**), synthesized from D-glutamic acid, was converted into unsaturated amino acid **50** as outlined in Scheme 13 (Chiou et al., 2000). The lipidic amino alcohol **51**, prepared from the reduction of **50** (Kokotos and Noula, 1996) was used as backbone for the synthesis of the lipophilic α-keto amide inhibitor **52**. This inhibitor formed a stable monomolecular film at the air/water interface. Inhibition studies using the monomolecular film technique with mixed films of 1,2-dicaprin containing variable proportions of the inhibitor showed a 50% decrease in pancreatic lipase activity at a 0.14 molar fraction.

In recent years, the pyridinium cross-links (+)-pyridinoline and (+)-deoxypyridinoline have gained much attention due to their potential clinical utility in the diagnosis of osteoporosis and other bone diseases. An efficient synthesis of *tert*-butyl (2*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-(2-oxiranyl) butanoate **55**, the key synthon for the preparation of collagen cross-links pyridinoline and deoxypyridinoline was described (Scheme 14) (Adamczyk et al., 1999a). The strategy for the synthesis of this epoxide was based on the extension of aldehyde **5** via a Wittig reaction to the olefin **53** using the ylide generated from methyltriphenylphosphonium bromide and n-BuLi. Selective removal of one of the two Boc groups of **53** was accomplished by treatment with TFA, without observing noticeable hydrolysis of the *tert*-butyl ester. Finally, oxidation of olefin **54** with m-CPBA produced the desired epoxide in 91% yield as 1:1 diastereomeric mixture. The second key synthon of deoxypyridinoline is the iodide **57**. Hydroboration of the olefin **54** using diborane-THF complex gave alcohol **56**. The hydroxyl group of **56** was converted to the iodide **57** using triphenylphosphine, iodine and imidazole.

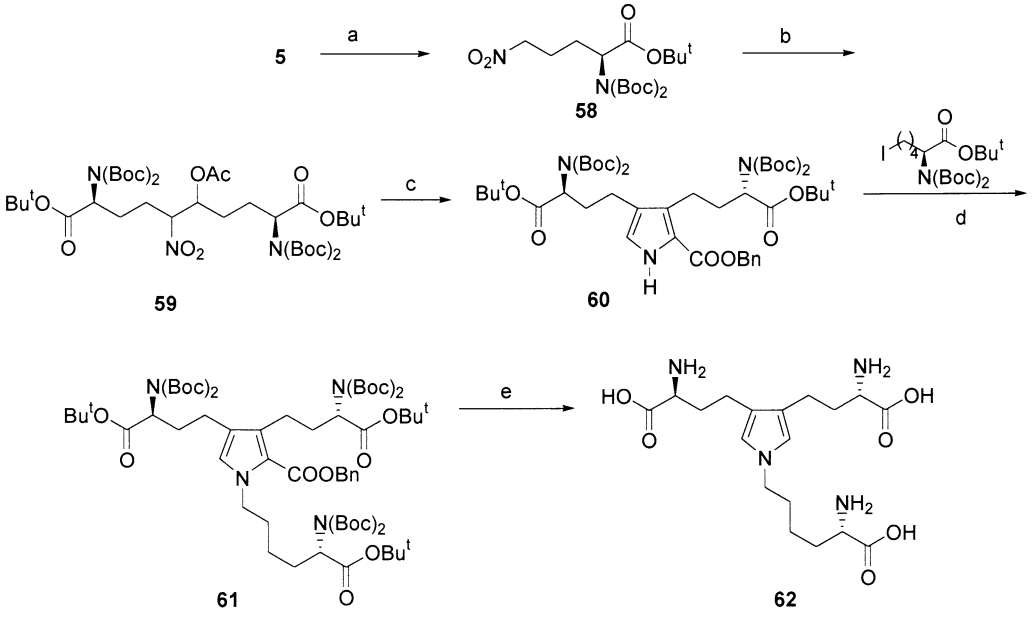
The total synthesis of (+)-deoxypyrrololine was accomplished as described in Scheme 15 (Adamczyk et al., 1999b, Adamczyk et al., 2001a). Condensation of **5** with nitro compound **58** and subsequent acetylation afforded α-acetoxynitro compound **59**. Subsequent condensation and cyclization with benzyl isocyanate in the presence of DBU gave the pyrrole intermediate **60**. *N*-Alkylation of **60** with **57** followed by removal of the protective groups and decarboxylation afforded the cross-link **62**.

Isotopically labelled (+)-deoxypyridinoline (**66**) is necessary as internal standard for quantification of collagen cross-links and is critical for the correlation of various immunoassay methods. Its synthesis was



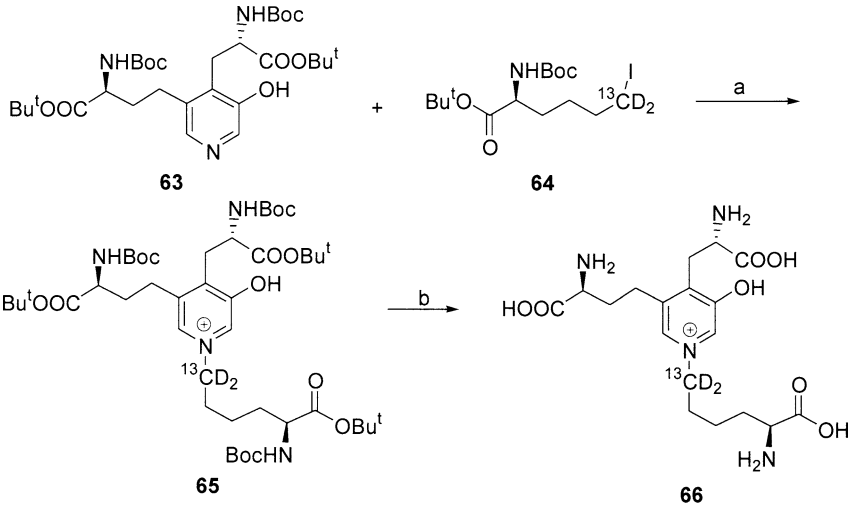
a) CH_3PPh_3Br, *n*-BuLi, THF, -78°C; b) TFA, CH_2Cl_2; c) *m*-CPBA, CH_2Cl_2; d) B_2H_6, THF, 0°C; e) I_2, PPH_3, Imidazole, THF

Scheme 14



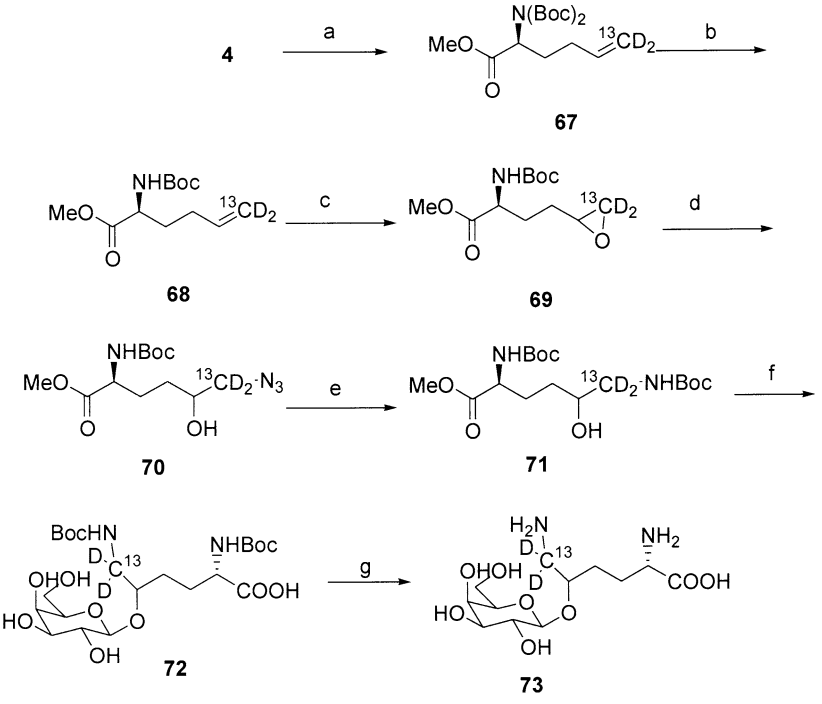
a) i.$NaBH_4$, MeOH, ii.I_2, PPh_3, THF, iii.$NaNO_2$, DMF; b) i.**5**, DMAP, CH_2Cl_2, ii.Ac_2O, DMAP, THF; c) $CNCH_2COOBn$, DBU, THF; d) *t*BuOK, [18]crown-6, THF; e) i.TFA/H_2O, ii.10%Pd/C, H_2, MeOH, iii. TFA

Scheme 15



a) 1,4-dioxane; b) TFA/H_2O

Scheme 16

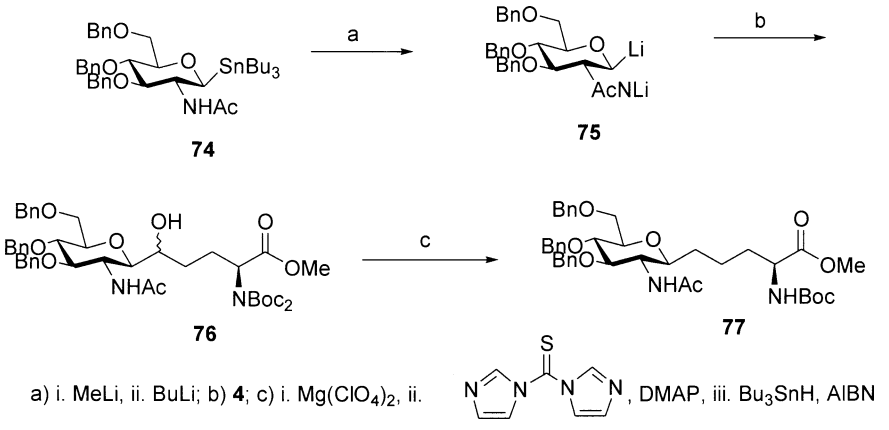


a) $^{13}CD_3PPh_3Br$, KHMDS, $C_6H_5CH_3$, -78°C; b) TFA, CH_2Cl_2; c) *m*-CPBA, CH_2Cl_2; d)NaN_3, MeOH, H_2O; e) 10%Pd/C, H_2, $(Boc)_2O$, EtOAc; f) i. acetobromo-α-D-galactose, $Hg(CN)_2$, toluene, ii. LiOH, THF, H_2O; g) TFA, CH_2Cl_2.

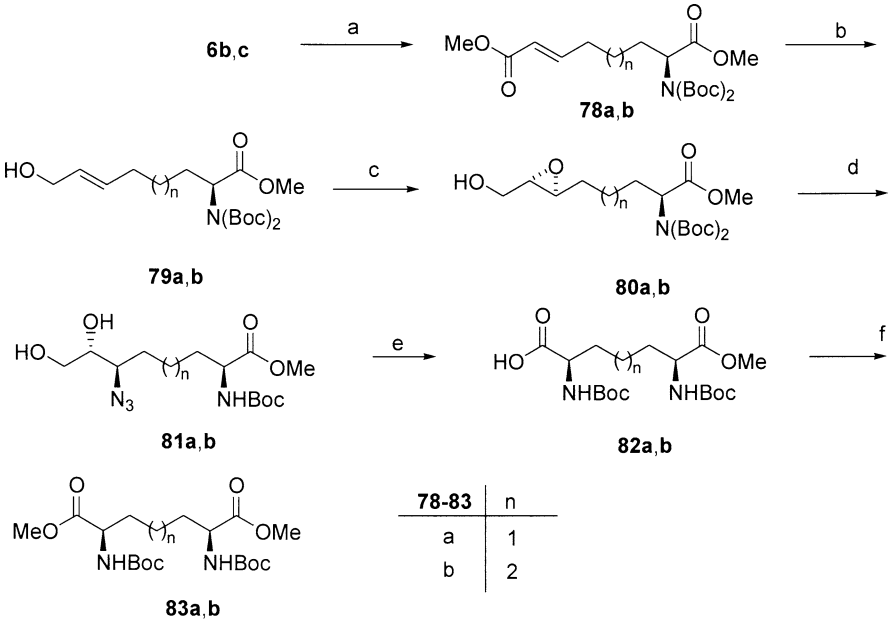
Scheme 17

achieved via quaternization of **63** with isotopically labelled iodide **64** and subsequent hydrolysis (Scheme 16) (Adamczyk et al., 2000). Iodide **64** was prepared from aldehyde **4** via a Wittig reaction with the ylide generated from a labelled ($^{13}CD_3$)-methyl triphenylphosphonium iodide.

Galactosylhydroxylysine is a structural component of bone collagen, which is formed by post-translational glycosylation of hydroxylysine. The synthesis of isotopically labelled galactosylhydroxylysine, which is useful as internal standard in immunoassays for the diagnosis of osteoporosis, is outlined in Scheme 17



Scheme 18

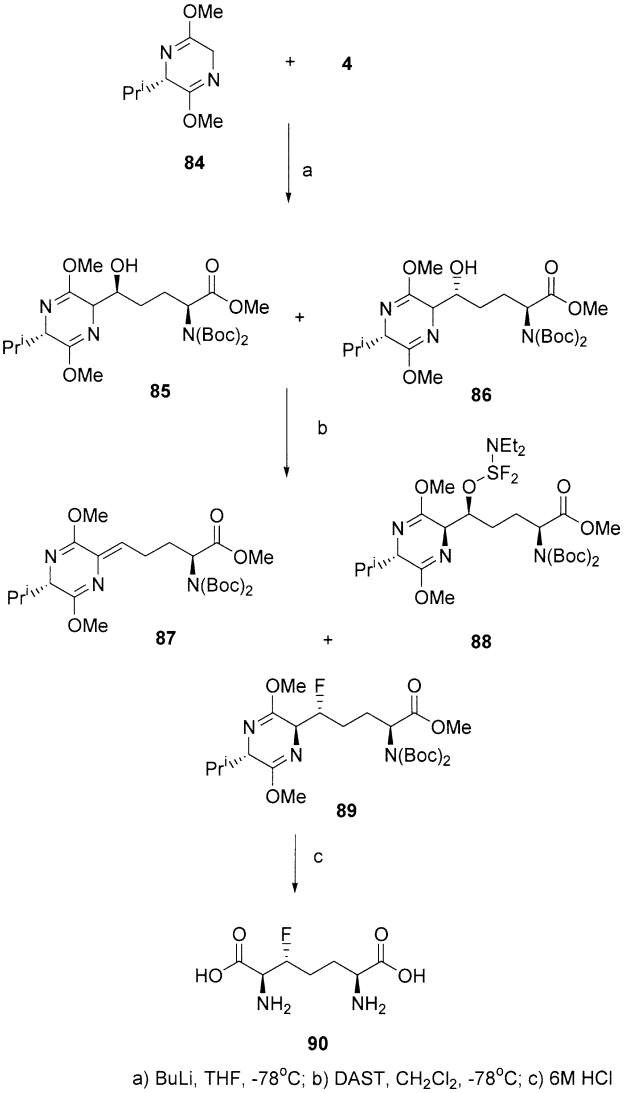


Scheme 19

(Adamczyk et al., 2001b). The labelled hydroxylysine derivative **71** was prepared from **4** with the introduction of label $^{13}CD_2$ via a Wittig reaction using $^{13}CD_3PPh_3I$. Glycosylation of **71** with acetobromo-α-D-galactose and subsequent hydrolysis afforded labelled galactohydroxylysine **73**.

The stereoselective synthesis of a C-glycosidic analogue of *N*-glucoasparagine was reported (Burkhart et al., 1997). The tin derivative **74** was first deprotonated with MeLi and then transmetalated with BuLi (Scheme 18). After addition of the aldehyde **4** the two diastereomeric C-glycosidic amino acids **76** were obtained in equimolar amounts. One Boc group was removed and the hydroxy group was transformed to the corresponding thiocarbonylimidazole. Radical reduction with Bu_3SnH and AIBN gave the desired amino acid **77** with pure β-configuration at the C-1.

In recent years, considerable attention has been focused on α,α′-diamino dicarboxylic acids because of their presence in living organisms or as isosteric analogues to improve the chemical stability of biologically active compounds. *N*,*N*-di-Boc-glutamate semialdehydes have found applications in the syn-

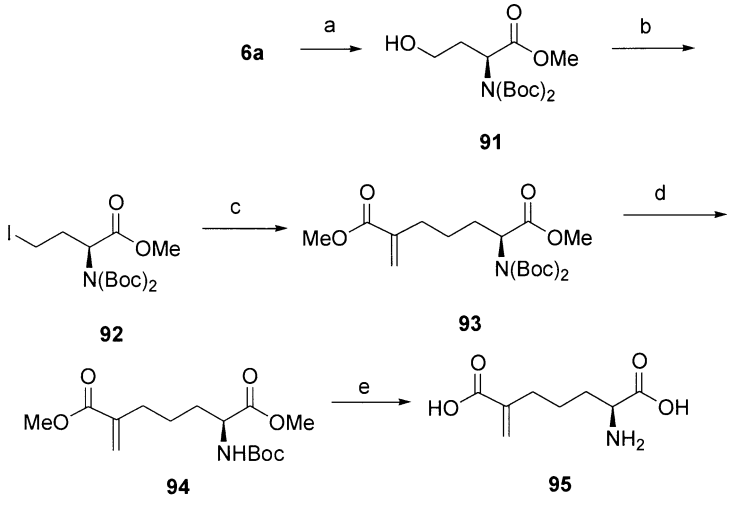


Scheme 20

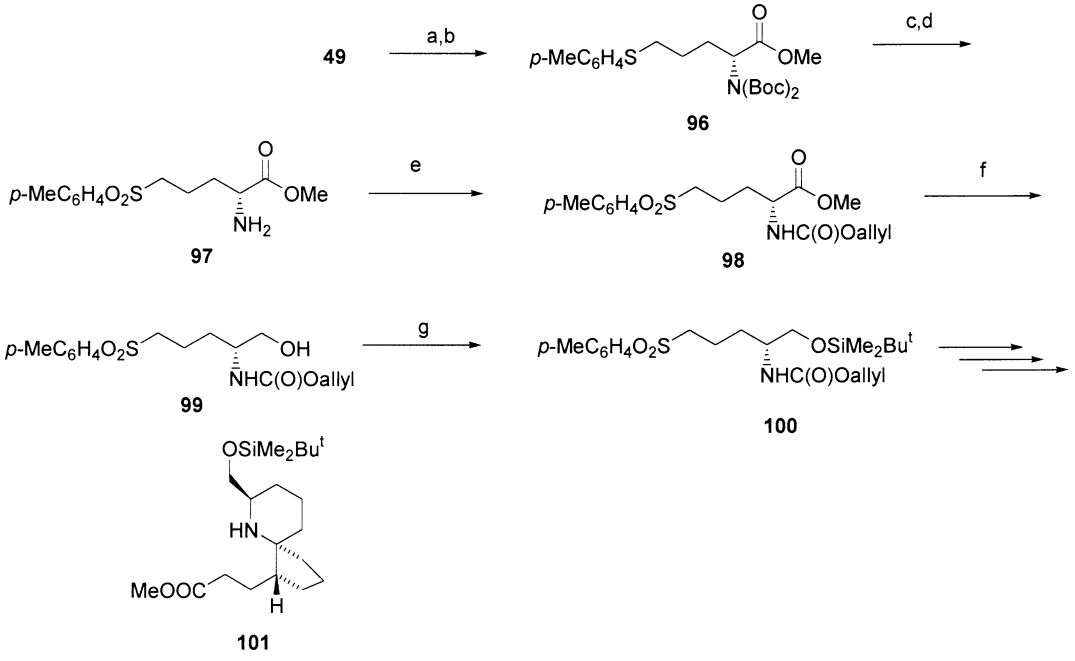
thesis of diamino diacids, such as 2,6-diaminopimelic and 2,7-diaminosuberic acids. In one synthetic procedure, aldehydes **6b**,**c** were used for the synthesis of the corresponding allylic alcohols **79**, which were used in a Katsuki-Sharpless asymmetric epoxidation followed by regioselective opening with sodium azide to yield 3-azido-1,2-diols **81a**,**b** (Scheme 19) (Hernandez and Martin, 2001). After oxidative cleavage, diamino diacids derivatives **83** were obtained in optically pure form.

A potent inhibitor of DAP epimerase, (2*S*,3*R*,6*S*)-3-fluoro-2,6-diaminopimelic acid (**90**), was synthesized starting from aldehyde **4**, after addition to the anion of (3*S*)-3,6-dihydro-2,5-dimethoxy-3-(1-methylethyl) pyrazine. Treatment with freshly distilled DAST permitted isolation of only the dehydrated compound **87**, which is presumably formed by base elimination of the activated intermediate **88**. However, use of DAST contaminated with water gave the fluoro derivative **89** as a single diastereomer in 52% yield with only trace amounts of the dehydrated product **87** (Scheme 20) (Sutherland and Vederas, 1999).

Another potent inhibitor of DAP dehydrogenase, which contains a planar α-carbon but lacks the characteristic basic nitrogen at the presumed reactive end of the molecule, was synthesized starting from aldehyde **6a** (Scheme 21) (Sutherland et al., 1999). This aldehyde was reduced to alcohol **91** and then converted into iodide **92**. Radical coupling of iodide **92** with stannane MeOOCC($=$CH$_2$)CH$_2$SnPh$_3$ was initiated thermally with AIBN to give α-aminopimelic acid analogue **93**. Selective removal of one out of the

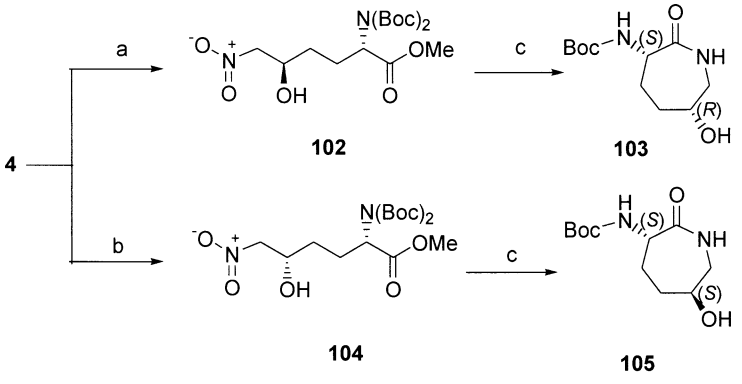


Scheme 21



a) $NaBH_4$, MeOH, THF, 0°C; b) (p-$MeC_6H_4S)_2$, Bu_3P, CH_2Cl_2; c) OsO_4, NMO, THF, $(CH_3)_2CO$, H_2O; d) CF_3COOH, Me_2S, CH_2Cl_2; e) allylOCO(O)Cl, pyridine, 0°C; f) $NaBH_4$, $CaCl_2$, EtOH, THF; g) $^tBuMe_2SiCl$, imidazole, THF

Scheme 22

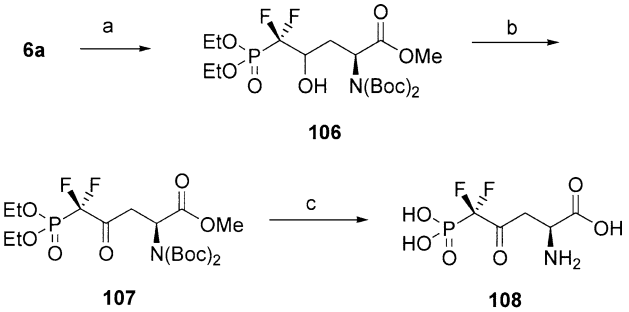


a) (*S*)-LLB, CH_3NO_2, THF, -40°C; b) (*R*)-LLB, CH_3NO_2, THF, -40°C; c) i. H_2, 10% Pd/C, MeOH, ii. 37% HCl, iii. Et_3N, Boc_2O, 50°C

Scheme 23

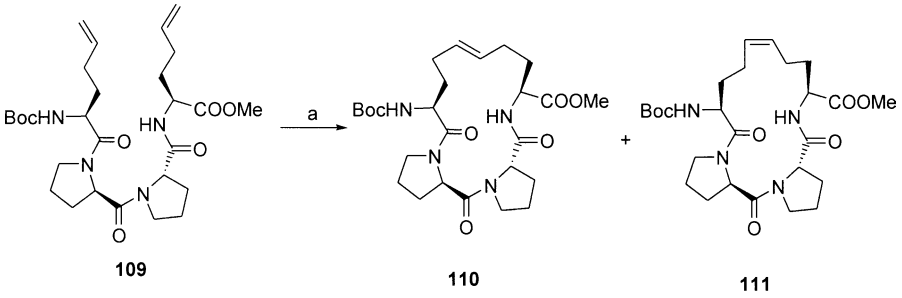
two Boc groups, and subsequent removal of all the protective groups gave amino acid **95**.

Halichlorine inhibits the expression of vascular cell adhesion molecule-1 (VCAM-1), which may be important in the recruitment of mononuclear lymphocytes to inflamed tissue. A route to the spirobicyclic core of halichlorine was reported starting from aldehyde **49** through a number of steps, as outlined in Scheme 22 (Clive and Yeh, 1999). Aldehyde **49** was reduced into alcohol, which was converted into the corresponding (*p*-methylphenyl)thio derivative **96**. Oxidation to the corresponding sulfone, followed by deprotection of



a) $(EtO)_2P(O)CF_2SiMe_3$, THF, 10%mol TBAF; b) Dess-Martin periodinane, CH_2Cl_2; c) TMSI, then aq. KOH, then Dowex AG50 WX8.

Scheme 24



Scheme 25

the nitrogen gave amine **97**, which was then protected again, now as an allyl carbamate **98**. The methyl ester **98** was reduced into alcohol **99** and the resulting alcohol was silylated to afford compound **100**, which was further used to prepare the spirobicyclic core of halichlorine, compound **101**.

Aldehyde **4** was used for the stereoselective synthesis of 2-amino-5-hydroxycaprolactam, which is an important constituent of a recently identified anti-tumor agent belonging to the bengamide marine sponge natural products. Nitro-aldol reaction of **4** with nitromethane in the presence of 10% of (*S*)-lanthanium-lithium-BINOL catalyst (LLB) gave the nitro-aldol adduct **102** (Scheme 23) (Roche et al., 2001). Reduction of the nitro group using 10% Pd/C, provided (2*S*,5*R*)-5-hydroxylysine, which was directly deprotected, cyclized and reprotected to give compound **103**. Similarly, compound **105** was prepared using the (*R*)-LLB catalyst in the first step of the synthesis.

A specific aspartate semi-aldehyde dehydrogenase inhibitor, the difluoromethylene analogue **108** of aspartyl phosphate, has been prepared using aldehyde **6a** (Scheme 24) (Cox et al., 2001). The most favorable conditions required the use of 1.3 eq. of $(EtO)_2P(O)CF_2SiMe_3$, 10% TBAF and one equivalent of aldehyde **6a**. The resulting diastereomeric alcohols **106** were oxidized into ketone **107**, which was deprotected to afford difluoromethylene analogue **108**.

Most recently, the synthesis of the tetrapeptide **109** from *S*-butenyl glycine and D-Pro-L-Pr-OH was accomplished in a straightforward manner using aldehyde **4** (Hanessian and Angiolini, 2002). Ring-closing metathesis with the Grubbs catalyst afforded the macrocyclized olefinic products **110** and **111** as a 1:1 mixture of *cis* and *trans* isomers in 92% yield (Scheme 25).

Conclusion

The synthetic applications of *N*,*N*-di-Boc-glutamate semialdehydes and related aldehydes summarized in this review article clearly demonstrate that these aldehydes are extremely useful chiral synthons. Their value is due to their easy preparation from natural α-amino acids in enantiomerically pure form and their simple structure that allows them to be used for many targets in organic synthesis.

References

Adachi K, Kohara T, Nakao N, Arita M, Chiba K, Mishina T, Sasaki S, Fujita T (1995) Design, synthesis and structure-activity relationship of 2-substituted-2-amino-1,3-propanediols: discovery of a novel immunosuppresant, FTY720. Bioorg Med Chem Lett 5: 853–856

Adamczyk M, Johnson DD, Reddy RE (1999a) Collagen cross-links: a convenient synthesis of *tert*-butyl-(2*S*)-2-[(*tert*-butoxycarbonyl)amino]-4-(2-oxiranyl)butanoate. Tetrahedron: Asymmetry 10: 775–781

Adamczyk M, Johnson DD, Reddy RE (1999b) Total synthesis of (+)-deoxypyrrololine: a potential biochemical marker for diagnosis of osteoporosis. Angew Chem Int Ed 38: 3537–3539

Adamczyk M, Johnson DD, Reddy RE, Rege SD (2000) Synthesis of isotopically labelled (+)-deoxypyridinoline. J Labelled Cpd Radiopharm 43: 463–472

Adamczyk M, Johnson DD, Reddy RE (2001a) Bone collagen cross-links: a convergent synthesis of (+)-deoxypyrrololine. J Org Chem 66: 11–19

Adamczyk M, Reddy RE, Rege SD (2001b) Synthesis of labelled galactosylhydroxylysine. J Labelled Cpd Radiopharm 44: 185–195

Bold G, Steiner H, Moesch L, Walliser B (1990) Preparation of semialdehyde derivatives of aspartic and glutamic acid *via* the Rosenmund reduction. Helv Chem Acta 73: 405–410

Burkhart F, Hoffmann M, Kessler H (1997) Stereoselective synthesis of a C-glycosidic analog of *N*-glucoasparagine. Angew Chem Int Ed Engl 36: 1191–1192

Chen W, Schoen FJ, Levy RJ (1994) Mechanism of efficacy of 2-amino oleic acid for inhibition of calcification of glutaraldehyde-pretreated porcine bioprosthetic heart valves. Circulation 90: 323–329

Chiou A, Markidis T, Constantinou-Kokotou V, Verger R, Kokotos G (2000) Synthesis and study of a lipophilic α-keto amide inhibitor of pancreatic lipase. Org Lett 2: 347–348

Clive DLJ, Yeh VSC (1999) Synthesis of a 6-azaspiro[4.5]decane related to halichlorine and the pinnaic acids. Tetrahedron Lett 40: 8503–8507

Constantinou-Kokotou V, Kokotos G (1999) Synthesis of optically active lipidic α-amino acids and lipidic 2-amino alcohols. Amino Acids 16: 273–285

Constantinou-Kokotou V, Magrioti V, Markidis T, Kokotos G (2001) Synthesis of enantiopure non-natural α-amino acids using *tert*-butyl (2*S*)-2-[bis-(*tert*-butoxycarbonyl)amino]-5-oxopentanoate as key-intermediate. The first synthesis of (*S*)-2-amino-oleic acid. J Pept Res 58: 325–331

Cox RJ, Hadfield AT, Belen Mayo-Martin M (2001) Difluoromethylene analogues of aspartyl phosphate: the first synthetic inhibitors of aspartate semi-aldehyde dehydrogenase. Chem Commun 1710–1711

Del Olmo E, Alves M, Lopez JL, Inchaustti A, Yaluff G, de Arias AR, San Feliciano A (2002) Leismanicidal activity of some aliphatic diamines and amino-alcohols. Bioorg Med Chem Lett 12: 659–662

Garner P, Park JM (1992) 1,1-Dimethylethyl (*S*) or (*R*)-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate: a useful serinal derivative. Org Synth 70: 18

Gosselin F, Lubell WD (1998) An olefination entry for the synthesis of enantiopure α,ω-diaminodicarboxylates and azabicyclo[*X*.*Y*.0] alkane amino acids. J Org Chem 63: 7463–7471

Hanessian S, Angiolini M (2002) Conformationally stable and constrained macrocarbocyclic pseudopeptide mimics of β-hairpin structures. Chem Eur J 8: 111–117

Hernandez N, Martin VS (2001) General stereoselective synthesis of chemically differentiated α-diamino acids: synthesis of 2,6-diaminopimelic and 2,7-diaminosuberic acids. J Org Chem 66: 4934–4938

Hirose R, Hamamichi N, Kitao Y, Matsuzaki T, Chiba K, Fujita T (1996) 2-Amnioalcohol immunosuppressants: structure-activity relationships. Bioorg Med Chem Lett 6: 2647–2650

Jurczak J, Golebiowski A (1989) Optically active *N*-protected α-amino aldehydes in organic synthesis. Chem Rev 89: 149–164

Kokotos G (1990) A convenient one-pot conversion of *N*-protected amino acids and peptides into alcohols. Synthesis 299–301

Kokotos G, Constantinou-Kokotou V (1992) Modified amino acids and peptides. Part 2. A convenient conversion of amino and peptide alcohols into amines. J Chem Res (S): 391

Kokotos G, Noula C (1996) Selective one-pot conversion of carboxylic acids into alcohols. J Org Chem 61: 6994–6996

Kokotos G, Constantinou-Kokotou V, Noula C, Nicolaou A, Gibbons WA (1996a) Synthesis of lipidic amino acid and dipeptide inhibitors of human platelet phospholipase A_2. Int J Peptide Protein Res 48: 160–166

Kokotos G, Martin V, Constantinou-Kokotou V, Gibbons WA (1996b) Synthesis of medicinally useful lipidic α-amino acids, 2-amino alcohols and diamines. Amino Acids 11: 329–343

Kokotos G, Padron JM, Noula C, Gibbons WA, Martin VS (1996c) A general approach to the enantiomeric synthesis of lipidic α-amino acids, peptides and vicinal amino alcohols. Tetrahedron: Asymmetry 7: 857–866

Kokotos G, Padron JM, Martin T, Gibbons WA, Martin VS (1998a) A general approach to the asymmetric synthesis of unsaturated lipidic α-amino acids. The first synthesis of α-amino arachidonic acid. J Org Chem 63: 3741–3744

Kokotos G, Theodorou V, Constantinou-Kokotou V, Gibbons WA, Roussakis C (1998b) Synthesis and in vitro cytotoxicity of lipophilic platinum(II) complexes. Bioorg Med Chem Lett 8: 1525–1530

Kokotos G, Constantinou-Kokotou V, Noula C, Hadjipavlou-Litina D (1999) Synthetic routes to lipidic diamines and amino alcohols: A class of potential antiinflammatory agents. Lipids 34: 307–311

Liang X, Andersch J, Bols M (2001) Garner's aldehyde. J Chem Soc Perkin Trans 1 2136–2157

Lucas R, Ubeda A, Paya M, Alves M, del Olmo E, Lopez JL, San Feliciano A (2000) Synthesis and enzyme inhibitory activities of a series of lipidic diamine and aminoalcohol derivatives on cytosolic and sectetory phospholipases A_2. Bioorg Med Chem Lett 10: 285–288

Magrioti V, Constantinou-Kokotou V (2002) Synthesis of (*S*)-α-amino-oleic acid. Lipids 37: 223–228

Markidis T, Kokotos G (2001) A novel approach to the synthesis of chiral terminal 1,2-diamines. J Org Chem 66: 1919–1923

Markidis T, Kokotos G (2002) Synthesis of enantiopure ω-functionalized C15 α-amino carboxylates. J Org Chem 67: 1685–1688

Markidis T, Padron JM, Martin VS, Peters GJ, Kokotos G (2001) Synthesis and *in vitro* cytotoxicity of long chain 2-amino alcohols and 1,2-diamines. Anticancer Res 21: 2835–2839

Meffre P (1999) Syntheses of optically active 2-amino-4-oxobutyric acid and *N*,*O*-protected derivatives. Amino Acids 16: 251–272

Nicolaou A, Kokotos G, Constantinou-Kokotou V, Charitos C, Noula C, Verger R, Gibbons WA (1997) Synthesis and properties of novel lipopeptides and lipid mimetics. J Peptide Sci 3: 291–298

Noula C, Constantinou-Kokotou V, Nicolaou A, Gibbons WA, Kokotos G (1996) Lipid mimetics as inhibitors of human platelet phospholipase A_2. Biochem Soc Trans 24: 303S

Padron JM, Kokotos G, Martin T, Markidis T, Gibbons WA, Martin VS (1998) Enantiospecific synthesis of α-amino acid semialdehydes: a key step for the synthesis of unnatural unsaturated and saturated α-amino acids. Tetrahedron: Asymmetry 9: 3381–3394

Reetz M (1991) New approaches to the use of amino acids as chiral building blocks in organic synthesis. Angew Chem Int Ed Engl 30: 1531–1546

Reetz M (1999) Synthesis and diastereoselective reactions of *N*,*N*-dibenzylamino aldehydes and related compounds. Chem Rev 99: 1121–1162

Roche D, Prasad K, Repic O, Blacklock TJ (2001) Stereoselective synthesis of 2-amino-5-hydroxycaprolactams from L-glutamic acid. Tetrahedron Lett 42: 1459–1462

Sutherland A, Vederas JC (1999) The first isolation of an alkoxy-*N*,*N*-dialkylaminodifluorosulfane from reaction of an alcohol and DAST: an efficient synthesis of (2S,3R,6S)-3-fluoro-2,6-diaminopimelic acid. Chem Commun 1739–1740

Sutherland A, Caplan JF, Vederas JC (1999) Unsaturated α-aminopimelic acids as potent inhibitors of *meso*-diaminopimelic acid (DAP) D-dehydrogenase. Chem Commun 555–556

Yadav JS, Reddy BVS, Reddy KS, Reddy KB (2002a) Indium-mediated facile cleavage of the t-butoxycarbonyl group from di-t-butylimidodicarbonate. Tetrahedron Lett 43: 1549–1551

Yadav JS, Reddy BVS, Reddy KS (2002b) Efficient and selective cleavage of t-butoxycarbonyl group from carbamates and amides by $CeCl_3 \cdot 7H_2O$-NaI. Synlett 468–470

Authors' address: Prof. Violetta Constantinou-Kokotou, Chemical Laboratories, Agricultural University of Athens, Iera Odos 75, 11855 Athens, Greece, E-mail: vikon@aua.gr