Amino Acids (1996) 11: 329–343

Amino
Acids

Synthesis of medicinally useful lipidic α-amino acids, 2-amino alcohols and diamines

Review Article

G. Kokotos[1], V. Martin[2], V. Constantinou-Kokotou[3], and W. A. Gibbons[4]

[1] Laboratory of Organic Chemistry, Department of Chemistry, University of Athens, Athens, Greece
[2] Instituto Universitario de Bio-Organica "Antonio Gonzalez", Universidad de La Laguna, Tenerife, Spain
[3] Chemistry Laboratory, Agricultural University of Athens, Athens, Greece
[4] University-Industry Centre for Pharmaceutical Research, The School of Pharmacy, University of London, London, England

Accepted, April 28, 1996

Summary. The lipidic α-amino acids (LAAs) are non-natural α-amino acids with saturated or unsaturated long aliphatic side chains. LAAs and their derivatives (lipid mimetics) together with the lipidic peptides represent a class of compounds which combine structural features of lipids with those of amino acids and peptides. Racemic LAAs may be prepared by classical methods and resolved by chemical or enzymatic methods. LAA amides and esters with saturated or unsaturated long chain amines and alcohols respectively, as well as lipidic dipeptide derivatives inhibit both pancreatic and human platelet phospholipase A_2. Lipophilic peptide derivatives are inhibitors of human neutrophil elastase. LAAs and their oligomers have been used as drug delivery system. A Lipid-Core-Peptide system has been designed and used as a combined adjuvant-carrier-vaccine system. A variety of lipid mimetics such as lipidic 2-amino alcohols, lipidic 1,2- and 1,3-diamines have been prepared based upon LAAs. Some of them are potent inhibitors of phospholipase A_2. A general approach to enantioselective synthesis of LAAs and lipid mimetics is based on the oxidative cleavage of 3-amino-1,2-diols obtained by the regioselective opening of enantiomerically enriched long chain 2,3-epoxy alcohols.

Keywords: Lipidic α-amino acids – Lipidic amino alcohols – Lipidic diamines – Enantioselective synthesis – Lipid mimetics – Drug delivery system – Phospholipase A_2 inhibitors

Abbreviations: Boc, *tert*-butoxycarbonyl; BSA, bovine serum albumin; CD, circular dichroism; DET, diethyl tartrate; DIBAL, diisobutyl aluminum

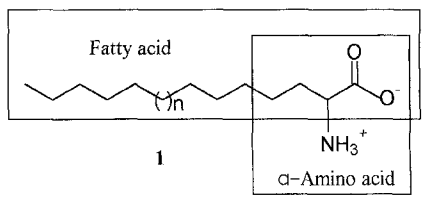
hydride; DMF, *N*,*N*-dimethylformammide; HMPA, hexamethylphosphoramide; HNE, human neutophil elastase; LAA, lipidic amino acid; LAAL, lipidic amino alcohol; LH-RH, luteinizing hormone-releasing hormone; LCP, lipid-core-peptide; LDA, lipidic diamine; LP, lipidic peptide; MAP, multiple antigenic peptide; PLA_2, phospholipase A_2; TBHP, *tert*-butyl hydroperoxide; THF, tetrahydrofuran; TRH, thyrotropin-releasing hormone; Z, benzyloxycarbonyl

Introduction

The lipidic α-amino acids (LAAs) are non-natural α-amino acids with saturated or unsaturated long aliphatic side chains (Scheme 1). The total number of carbon atoms varies from eight to twenty four. The aim of this review is to summarize the methods for the synthesis of lipidic α-amino acids, lipidic 2-amino alcohols, lipidic diamines and derivatives and the biological applications of these compounds.

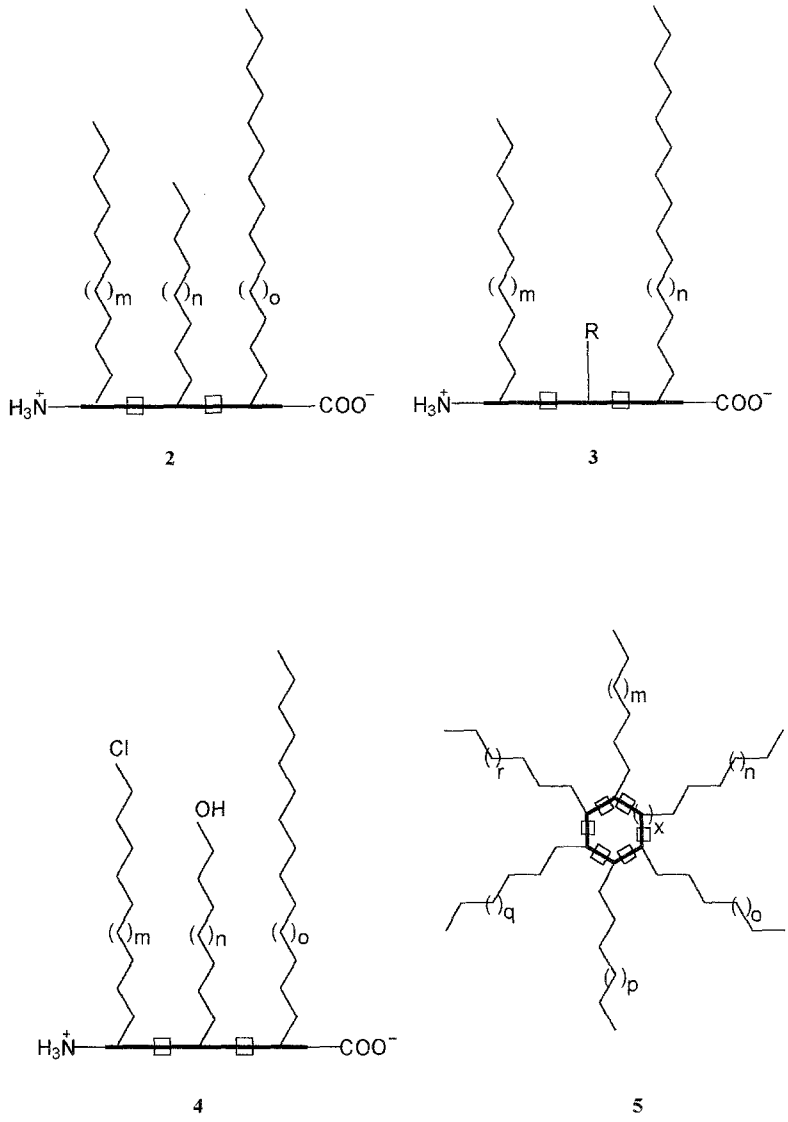
LAAs and their derivatives (lipid mimetics) together with the lipidic peptides (LPs) represent a class of compounds which combine structural features of lipids with those of amino acids and peptides (Gibbons, 1991). The dual nature of these compounds is reflected in their physical properties. They are highly lipophilic due to the long lipidic side chains, yet show polar, chemical and conformational behavior characteristic of amino acids and peptides. LPs can take up several forms including linear homo-oligomers, heteropeptides containing coded amino acids or substituted lipidic amino acids and cyclic liposome-like structures (Scheme 2).

The potential use of LAAs is wide: lubricants (Takino et al., 1987), cosmetics (Kitamura et al., 1987), polishes (Sagawa and Takehara, 1987a) and surface improvers for ceramics (Sagawa and Takehara, 1987b). In addition, LAAs and LPs could be useful as detergents and biocompatible and/or weather-proof coatings. However, of particular interest for us, is their use as a drug delivery system, as an adjuvant/carrier system and as starting materials for the synthesis of biologically active and medicinally interesting lipid mimetics. *Lipid mimetics* are defined as synthetic molecules that resemble natural lipids either in structure or in function; they may be glycerides, other lipids, sphingolipids, phospholipids or glycolipids.



1

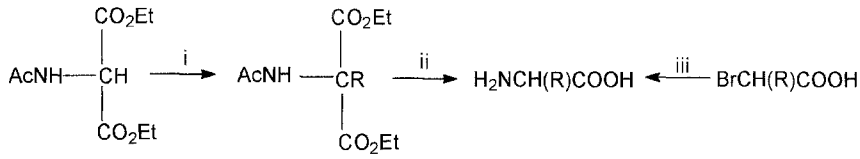
Scheme 1. Lipidic α-amino acid



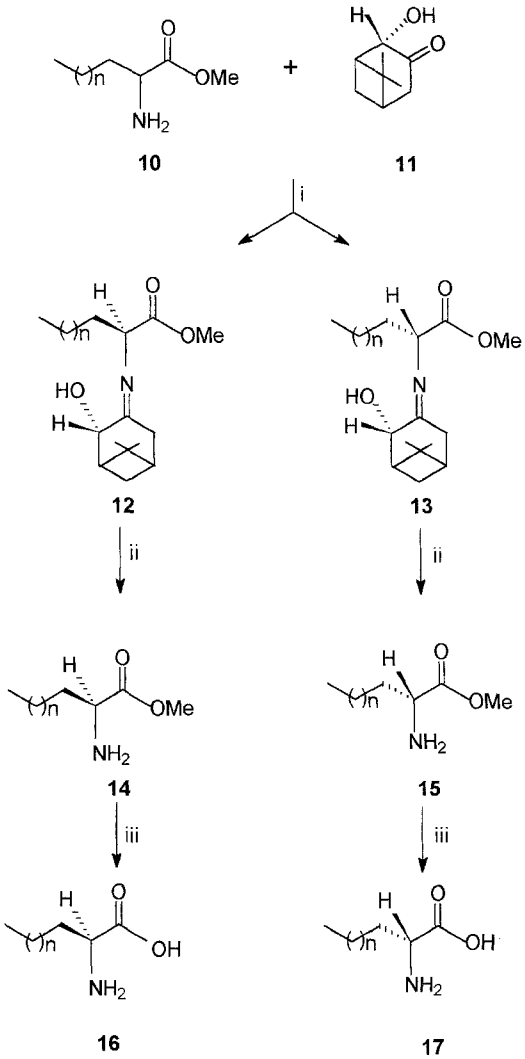
Scheme 2. **2** Homo-oligomers; **3** Hetero-peptides containing coded amino acids (R = residue of coded amino acid); **4** Hetero-peptides containing substituted LAAs; **5** Cyclic liposome-like structure; □ amide bond

Racemic LAAs and resolution

The chemical methods for the synthesis of α-amino acids have been summarized in some classical books concerning the chemistry of amino acids and peptides (Greenstein and Winitz, 1961; Roberts and Vellaccio, 1983; Barrett, 1985; Williams, 1989). Racemic LAAs can be prepared by classical methods as shown in Scheme 3. Diethyl acetamidomalonate (**6**) is treated with 1-bromoalkanes in the presence of sodium ethoxide and the alkyl diethyl acetamidomalonate intermediate **7** is hydrolyzed and partially decarboxylated by heating in hydrochloric acid (Gibbons et al., 1990; Mori and Funaki, 1985; Albertson, 1946). An alternative method is the reaction of



Scheme 3. *i* EtONa, RBr; *ii* HCl, reflux; *iii* NH_4OH



Scheme 4. *i* $BF_3{\cdot}Et_2O$; *ii* HCl, NH_2OH; *iii* NaOH

α-bromoalkanoic acids **9** with ammonium hydroxide (Birnbaum et al., 1953). The racemic compounds may be resolved by chemical or enzymatic methods.

Racemic lipidic amino acid methyl esters **10** are heated in toluene with the chiral α-pinene derivative (1*S*,2*S*,5*S*)-(-)-2-hydroxypinan-3-one (**11**) in the presence of a catalytic amount of boron trifluoride etherate (Gibbons et al.,

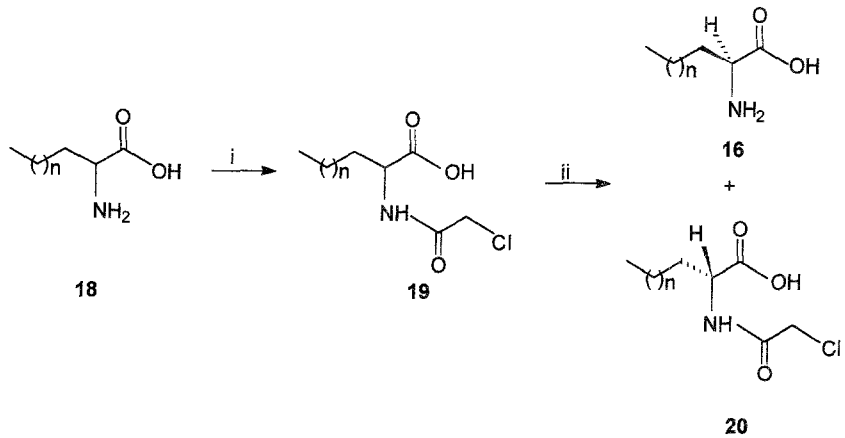
1990) (Scheme 4). The resulting diastereomeric Schiff bases **12**, **13** are separated by preparative thin-layer chromatography on silica gel or HPLC. The optically pure methyl esters **14**, **15** are obtained by hydroxylamine hydrochloride assisted hydrolysis of the Schiff bases. Saponification of the methyl esters yields optically active LAAs. The absolute configuration of the chemically resolved esters determined on the basis of the sign of the Cotton effect of the circular dichroism (CD) spectra; those exhibiting positive ones are assigned the (*S*), those with a negative one, the (*R*) configuration.

In the enzymatic method, the racemic LAA is converted into the N-chloroacetyl derivative **19** (Scheme 5). The enzyme acylase I (Birnbaum et al., 1953) or *Aspergillus* amino acylase (Mori and Funaki, 1985) specifically hydrolyses the (*S*)-N-chloroacetyl derivative to yield the (*S*)-amino acid **16**. The (R) enantiomer can be obtained by treatment of the remaining solution with hydrochloric acid.

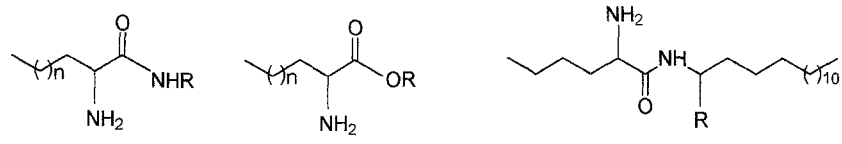
Fully protected homo-oligomers of LAAs may be prepared by the conventional methods of peptide synthesis in solution. Racemic dimers up to octamers have been prepared (Gibbons et al., 1990; Gibbons, 1991) by coupling of N-*tert*-butoxycarbonyl (Boc) protected LAAs with the appropriate lipidic amino acids methyl esters using the method of 3-[3-(dimethylamino)-propyl]-1-ethyl carbodiimide in the presence of 1-hydroxybenzotriazole. The LAA oligomers exhibit poor solubility characteristics with increasing molecular weight. To improve the solubility of the peptides and to modify their degradation/biodegradation characteristics several C- and/or N-protected hetero-oligomers containing either coded amino acids or ω-derivatised LAAs have been prepared.

Enzyme inhibitors

LAA amides **21** with saturated or unsaturated long chain amines as well as LAA esters **22** with saturated or unsaturated long chain alcohols (Scheme 6) have been synthesized (Kokotos et al., 1996a) and exhibited interesting bio-



Scheme 5. *i* $ClCH_2COCl$, NaOH; *ii* acylase



21 22 23

Scheme 6. 21, 22 R = saturated or unsaturated long chain; **23** R = COOMe, COOH, CH_2OH

logical properties. These classes of compounds inhibited both pancreatic (Nicolaou et al., 1995) and human platelet phospholipase A_2 (PLA_2) (Kokotos et al., 1996a) and are potential antiinflammatory agents. Comparable properties are exhibited by lipidic dipeptide derivatives **23** (Kokotos et al., 1996a; Nicolaou et al., 1995).

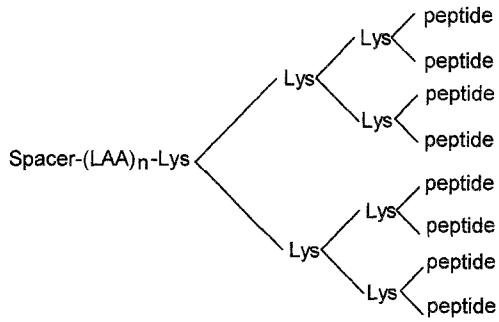
A series of lipophilic peptide derivatives of the general structure Boc-$(LAA)_n$-Ala-Ala-Pro-Val-OH were synthesized in keeping with the presence of an extended binding site in human neutrophil elastase (HNE) (Toth et al., 1995). *In vitro* studies showed that the compound containing three residues of LAA was a powerful inhibitor of HNE ($IC_{50} = 1.8 \times 10^{-10}$M). This derivative protected skin elastic fibres against degradation by HNE, when injected intradermally to rabbit dermis.

LAAs conjugates with drugs and bioactive peptides: stability, prodrugs and delivery

LAAs and their oligomers, because of their bifunctional nature, have the capacity to be chemically conjugated to drugs and bioactive peptides with a wide variety of functional groups. The linkage between drug or peptide and lipidic unit may either be biologically stable (such that a new drug is formed) or posses biological or chemical instability (when the conjugate will be a prodrug). In either case, the resulting conjugates would be expected to posses a high degree of membrane-like character, which may be sufficient to facilitate their passage across membranes. The long aliphatic side chains may also have the additional effect of protecting a labile parent drug or peptide from enzymatic attack. The lipidic system has been conjugated to a wide variety of different compounds: benzoquinolizine, β-lactam antibiotics, hydrophilic sugars, γ-aminobutyric acid, chlorambucil, morphine, peptides as TRH and LHRH. The use of LAAs and LPs as drug delivery system has been summarized in two reviews (Toth and Gibbons, 1992; Toth, 1994).

Adjuvant semisynthetic vaccines

Synthetic peptides are widely used to generate antibodies. To induce high antibody response, the low molecular weight peptide has to be conjugated to a carrier protein (BSA) and administrated with an appropriate adjuvant. High antibody response was observed when the peptides were incorporated into



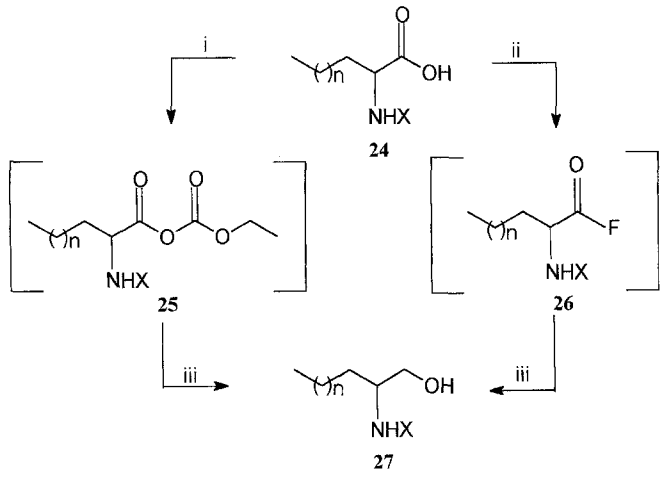
Scheme 7. Lipid-core-peptide system

polylysine to form Multiple Antigenic Peptide (MAP) (Tam, 1988, 1989). To attain higher antibody responses, the antigen must be anchored to the cell membrane, but the polylysine system is not lipophilic enough to fulfill this requirement. A novel Lipid-Core-Peptide (LCP) system has been developed (Toth et al., 1993) by incorporating LAAs to the polylysine system to enhance lipophilicity and membrane binding effects and the metabolic stability of the LCP system. This system was designed to combine the use of the branched polylysine and the lipophilic α-amino acid based anchor (Scheme 7) and was synthesized using standard automated solid phase peptide synthetic methods. Since this lipidic anchor also functioned as adjuvant, this system could be used as a drug delivery system or as a combined adjuvant-carrier-vaccine or -hormone system, where the "peptide" could be an epitope or potential vaccine, a hormone, or a nonpeptide system (drug) (Toth and Gibbons, 1993).

Sphingosine lipid analogues

Synthesis of lipidic amino alcohols (LAALs) based upon LAAs

Sphingosine and ceramide are the basic structural units of the sphingolipids which are essential membrane and cell wall constituents. A great number of such structural components have been found in animals, plants and microorganisms as a part of complex lipids, while free ceramides have been found in small amounts in plant and animal tissues (Christie, 1982). Although important biological functions of sphingolipids have been recognized (Sweeley, 1989; Fukaya et al., 1989), their functions are still being explored including the therapeutic potential of such analogues. Thus structural analogues for biological testing are required and a method for the synthesis of ceramide and sphingosine analogues from LAAs was developed. N-palmitoyl, N-acetyl and N-Boc protected LAAs **24** were converted directly into ceramide analogues **27** by chemoselective reduction of their corresponding mixed anhydrides **25** with sodium borohydride in tetrahydrofuran (THF) with dropwise addition of methanol (Kokotos, 1990; Kokotos et al., 1992) (Scheme 8). The *in situ* reduction of the mixed anhydrides was performed rapidly at 0°C in good yield. The peptide bond and the N-protecting groups remained unaffected under

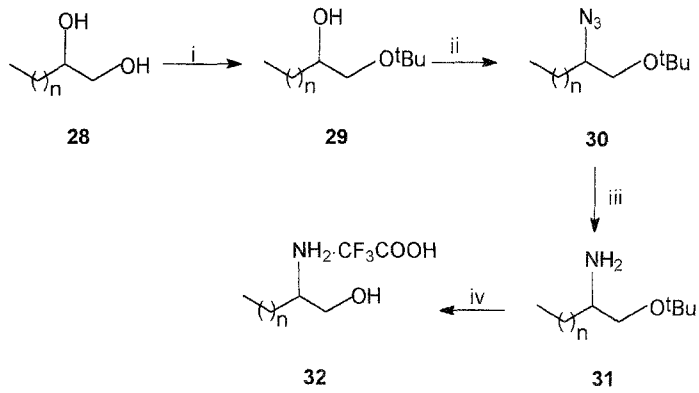


Scheme 8. *i* N-methylmorpholine, $ClCO_2Et$, THF; *ii* cyanuric fluoride, C_6H_5N; *iii* $NaBH_4$, MeOH

these conditions. An alternative method affording lipidic amino alcohols (LAALs) in higher yield is the *in situ* reduction of acyl fluorides **26** by sodium borohydride with dropwise addition of methanol (Kokotos and Noula, 1996). Acyl fluorides were obtained by treatment of carboxylic acids with cyanuric fluoride in the presence of pyridine.

Removal of the Boc-protecting group from N-protected amino alcohols using HCl in THF gave the sphingosine analogues. These analogues present special interest since sphingosine is a metabolic intermediate of sphingolipids that modulates the activity of several enzymes involved in signal transduction and cell growth, such as phospholipase A_2 and phospholipase D (Franson et al., 1992), protein kinase C (Hannun et al., 1986) and other kinases (Fiore et al., 1990; Kirshnamurti et al., 1989), phosphatidate phosphohydrolase (Mullmann et al., 1991) and several calmodulin – dependent enzymes (Jefferson and Schulman, 1988). LAALs found to inhibit reversibly pancreatic and human platelet PLA_2 (Noula et al., 1996). 2-Amino-octadecanol exhibited inhibitory activity (IC_{50} 4 μM) equal to that caused by sphingosine or phytosphingosine.

Another approach to lipidic 2-amino alcohols uses long chain 1,2-diols as starting material (Kokotos et al., unpublished data). Selective protection of the primary hydroxyl of 1,2-diols **28** by the *tert*-butyl group was achieved in good yield by treatment with *tert*-butyl trichloroacetimidate in the presence of a catalytic amount of boron trifluoride etherate (Scheme 9). The secondary hydroxyl of **29** was activated as the mesylate and converted directly into the azido group by treatment with sodium azide in N,N-dimethylformamide (DMF) in high yield. Reduction of the azido group of **30** using sodium borohydride in the presence of 10% palladium – charcoal (Kokotos and Constantinou-Kokotou, 1992) at room temperature afforded the O-protected 2-amino alcohol **31**. The *tert*-butyl group was removed by trifluoroacetic acid.

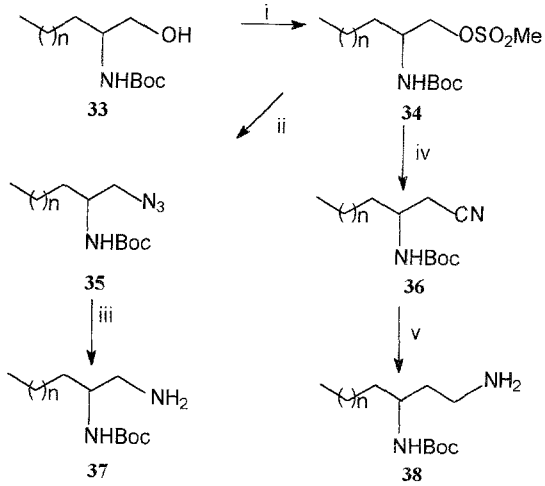


Scheme 9. *i* $Cl_3C(=NH)O^tBu$, $BF_3{\cdot}Et_2O$; *ii* $MeSO_2Cl$, Et_3N; NaN_3, DMF; *iii* $NaBH_4$, 10% Pd/C; *iv* CF_3COOH

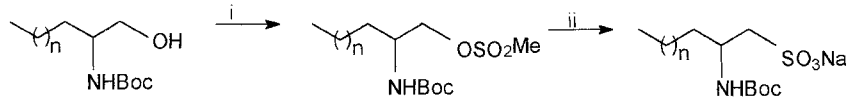
Lipidic diamines (LDAs) and taurines

The hydroxy group of Boc-protected amino alcohols **33** was activated by conversion into methanesulfonate **34** in high yield and then replaced by nitrogen nucleophiles leading to various amines (Scheme 10). Replacement of the mesyl group by the azido group gave amino azides **35** and after reduction 1,2-diamines **37** (Kokotos et al., 1992). Replacement by the cyano group yielded amino nitriles **36** and after reduction, 1,3-diamines **38** (Constantinou-Kokotou and Kokotos, 1994, 1995). Following both procedures selectively monoprotected diamines can be prepared. Several free lipidic diamines were tested and were potent inhibitors of PLA_2 (Noula et al., 1996).

LAALs can also be used as starting materials for the preparation of lipidic taurines. Taurines and analogues exhibit various interesting biological properties and were proposed as neuromodulators, neurotransmitters, indicators of hepatic cytotoxicity and as anti-convulsants. Replacement of the mesyl



Scheme 10. *i* $MeSO_2Cl$, Et_3N; *ii* NaN_3, DMF; *iii* $NaBH_4$, 10% Pd/C; *iv* NaCN, DMF; *v* $NaBH_4$, $NiCl_2$



33 34 39

Scheme 11. *i* $MeSO_2Cl$, Et_3N; *ii* Na_2SO_3

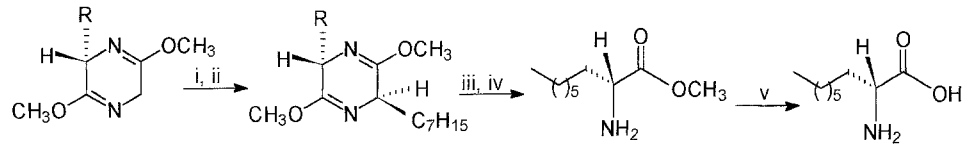
group of **34** by a sulfo group afforded long chain 2-substituted taurines **39** (Constantinou-Kokotou and Kokotos, 1995) (Scheme 11).

Enantioselective LAA synthesis

Methods to synthesize α-amino acids in optically active form have been reviewed by Williams and Duthaler (Williams, 1989; Duthaler, 1994). Some of them have been used for the synthesis of medium chain LAAs. The synthesis of (*R*)-2-aminononanoic acid **43** is based on the reaction of heptyl bromide with the lithiated bis-lactim ether either of cyclo(L-Val-Gly) **40a** (e.e 75–80%) (Schollkopf et al., 1981) or of cyclo(L-*tert*-Leu-Gly) **40b** (e.e. >95%) (Scheme 12) (Schollkopf and Neubauer, 1982).

Williams has reported the synthesis of (*S*)-2-amino-decanoic acid **47** (e.e. 98%) by the reaction of tri-*n*-butyltin acetylide **45** with the bromoglycinate **44** and subsequent catalytic hydrogenation (Scheme 13) (Zhai et al., 1988; Williams and Zhai, 1988).

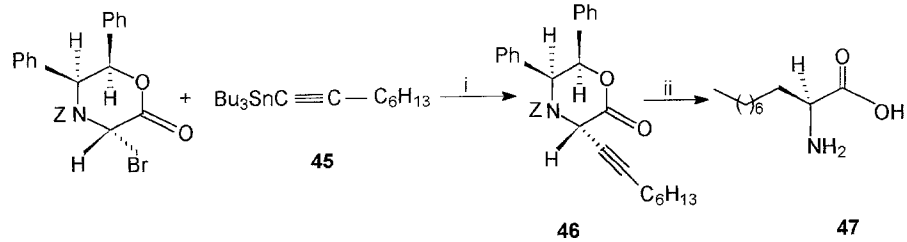
A general approach to the enantioselective synthesis of LAAs, LPs, LAALs etc. is based on the regioselective opening of chiral long chain 2,3-



40a,b 41a,b 42 43

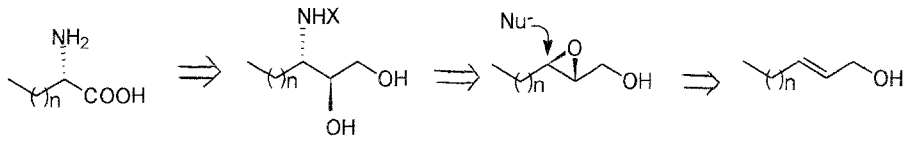
a: R = iPr
b: R = tBu

Scheme 12. *i* BuLi; *ii* $C_7H_{15}Br$; *iii* 0.25N HCl; *iv* NH_3, H_2O; *v* HCl 6N

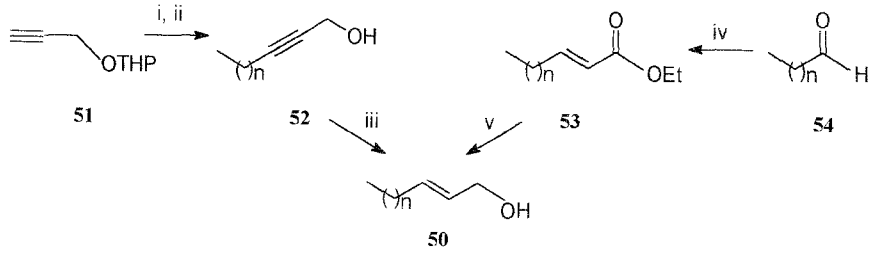


44 45 46 47

Scheme 13. *i* $ZnCl_2$; *ii* H_2, $PdCl_2$, 20 psi



Scheme 14

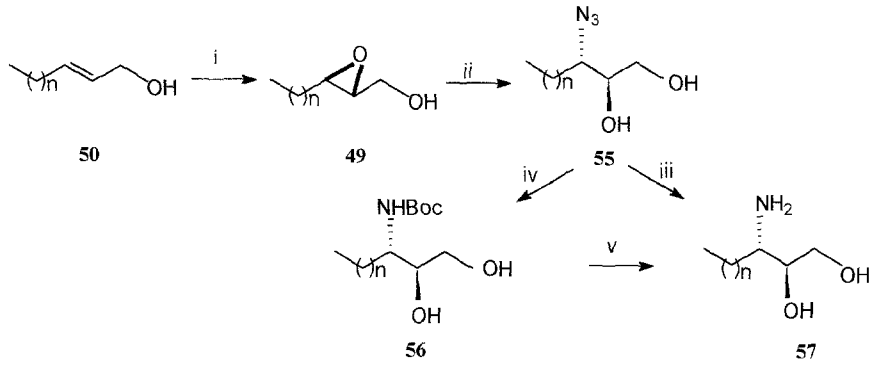


Scheme 15. *i* n-BuLi, $CH_3(CH_2)_nBr$; *ii* HCl, MeOH; *iii* $LiAlH_4$, THF; *iv* EtO_2CCH_2COOH, pyridine; *v* DIBAL

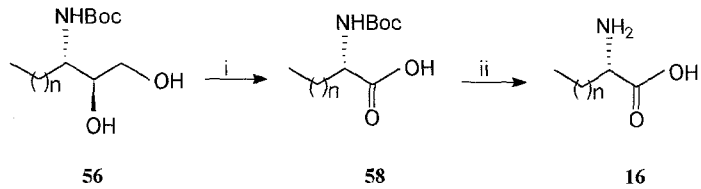
epoxy alcohols (Scheme 14) (Kokotos et al., 1996b). For this approach attention must be focused on two major points: a) The synthesis of the suitable precursor. The appropriate allylic alcohol **50** has to be chosen as the substrate for the asymmetric epoxidation using the proper chiral auxiliary. The final enantiomer of the α-amino acid depends on the use of (*R*,*R*) or (*S*,*S*)-dialkyl tartrate. b) The choice of the appropriate nitrogen containing nucleophile. It should be selected taking into consideration regioselectivity and yield of the opening reaction as well as facilities to transform such a group into the final amino group. The appropriate nucleophile should also be chosen to facilitate the cleavage of the C–C bond and thus generate the acid group in **16**.

Two main methodologies were used for the synthesis of the necessary allylic alcohol (Scheme 15). The first one was based on the alkylation of protected propargyl alcohol **51** and stereoselective reduction of the free propargylic alcohol using $LiAlH_4$. The second used either a Wittig-Horner reaction (Kelly, 1991), or a Knoevenagel condensation over a suitable aldehyde **54** (Tietze and Beifuss, 1991), to obtain the E-unsaturated ester **53** which is reduced with DIBAL or AlH_3 to the desired allylic alcohol **50**. Considering that the propargylic approach produced one homologation of three carbon atoms and the Witting-Horner or Knoevenagel approach extends the chain by two carbons, both methods are based on economic parameters considering the relative price of the precursor alkyl bromide or aldehyde.

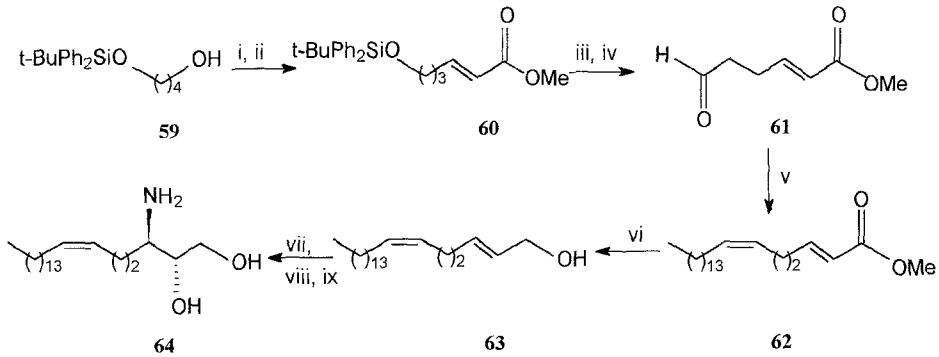
Allylic alcohols **50** were submitted to Sharpless epoxidation (Katsuki and Sharpless, 1980; Martin et al., 1981) (Scheme 16) and gave epoxides **49** in high yield and enantiomeric excesses (>80% yield and >95% ee). Because of the low solubility of long chain allylic alcohols in dichloromethane, the addition of such a precursor has to be slow enough to avoid precipitation that can dramatically decrease the enantiomeric purity and yield of the epoxide obtained.



Scheme 16. *i* $Ti(OPr\text{-}i)_4$, (*S*,*S*)-(−)-DET, TBHP, CH_2Cl_2; *ii* NaN_3, NH_4Cl, $MeOH:H_2O$; *iii* H_2, Pd *iv* H_2, $Pd(OH)_2$, $(Boc)_2O$; *v* HCl, THF



Scheme 17. *i* $NaIO_4$, $KMnO_4$, Na_2CO_3; *ii* HCl, THF



Scheme 18. *i* SO_3-Py, DMSO, CH_2Cl_2, Et_3N; *ii* Wittig – Horner; *iii* HF, CH_3CN; *iv* SO_3-Py; *v* $Ph_3P^+CH_2(CH_2)_{13}CH_3$, X^-, n-BuLi, THF, HMPA; *vi* DIBAL; *vii* $Ti(OPr\text{-}i)_4$, (*R*,*R*)(+)-DET, TBHP; *viii* NaN_3, NH_4Cl; *ix* $NaBH_4$, 10% Pd/C

The opening of epoxides (Caron and Sharpless, 1985; Caron et al., 1988) using sodium azide and ammonium chloride yielded azido diols **55** with good regioselectivity (>10:1) and yield. Reduction of the azido group under standard conditions gave the corresponding 3-amino-1,2-diols **57** in moderate yield. Alternatively, the simultaneous reduction of the azido group and N-Boc protection was more convenient either to obtain directly N-Boc protected amino diols **56** or hydrochlorides of free amines **57** since both steps are practically quantitative (Kokotos et al., 1996b).

N-Boc protected amino acids **58** were obtained in high yield (>85%) when 3-(N-butoxycarbonylamino)-1,2-diols **56** were submitted to oxidative cleav-

age using potassium permanganate (Scheme 17) (Lemieux and von Rudloff, 1955). Final deprotection of Boc group using HCl in THF yielded the chiral LAA **16**.

Unsaturated lipidic 3-amino-1,2-diols **64** may be obtained by the above described general methodology starting from the appropriate unsaturated allylic alcohol **63** (Scheme 18). However this methodology of obtaining unsaturated LAAs has a strong limitation, since the final step implies conditions that affect the double bonds. Further studies directed to obtain unsaturated LAAs with more than one double bond are now under development in our laboratories.

Acknowledgements

This research has been supported by the E.C. (Human Capital and Mobility, Contract No CT930288; BIO2-CT943041).

References

Albertson NFJ (1946) The synthesis of amino acids from ethyl acetamidomalonate and ethyl acetamidocyanoacetate. III. The use of primary halides. J Am Chem Soc 68: 450–453

Barrett GC (1985) Chemistry and biochemistry of the amino acids. Chapman and Hall, London

Birnbaum SM, Fu SCJ, Greenstein JP (1953) Resolution of the racemic α-amino derivatives of heptylic, caprylic, nonylic, decylic and undecylic acids. J Biol Chem 203: 333–338

Caron M, Sharpless K (1985) Ti-(O-i-Pr)$_4$ mediated nucleophilic openings of 2,3-epoxy alcohols. A mild procedure for regioselective ring opening. J Org Chem 50: 1557–1560

Caron M, Carlier PR, Sharpless K (1988) Regioselective azide opening of 2,3-epoxy alcohols by [Ti-(O-i-Pr)$_2$(N$_3$)$_2$]: Synthesis of α-amino acids. J Org Chem 53: 5185–5187

Constantinou-Kokotou V, Kokotos G (1994) Synthesis of 1,3-diamines. Org Prep Proc Int 26: 603–606

Constantinou-Kokotou V, Kokotos G (1995) Conversion of lipidic amino acids into lipidic 1,3-diamines and taurines. Amino Acids 9: 66–67

Christie WW (1982) Lipid analysis, 2nd edn. Pergamon Press, Oxford, p 13

Duthaler R (1994) Recent developments in the stereoselective synthesis of α-amino acids. Tetrahedron 50: 1539–1650

Fiore S, Nicolaou KC, Caulfield T, Kataoaka H, Serhan C (1990) Evaluation of synthetic sphingosine, lysosphingolipids and glycosphingolipids as inhibitors of functional responces of human neutrophils. Biochem J 266: 25–31

Franson R, Harris L, Ghosh S, Rosenthal M (1992) Sphingolipid metabolism and signal transduction: inhibition of *in vitro* phospholipase activity by sphingosine. Biochim Biophys Acta 1136: 169–174

Fukaya N, Ito M, Iwata H, Yamagata T (1989) Characterization of the glycosphingolipids of pig cortical bone and cartilage. Biochim Biophys Acta 1004: 108–116

Gibbons WA (1991) Preparation of racemic and optically -active fatty amino acids, their homo- and hetero-oligomers and conjugates, as pharmaceuticals. Brt Pat Appl GB 2217319 (April 19, 1988). Chem Abstr 114: 235105z

Gibbons WA, Hughes RA, Charalambous M, Christodoulou M, Szeto A, Aulabaugh AE, Mascani P, Toth I (1990) Synthesis, resolution and stuctural elucidation of lipidic amino acids and their homo- and hetero- oligomers. Liebigs Ann Chem: 1175–1183

Greenstein JP, Winitz M (1961) Chemistry of the amino acids. John Wiley and Sons, New York, pp 2381–2406

Hannun Y, Loomis C, Merrill A, Bell R (1986) Sphingosine inhibition of protein kinase C activity and phorbol dibutyrate binding *in vitro* and in human platelets. J Biol Chem 261: 12604–12609

Jefferson A, Schulman H (1988) Sphingosine inhibits calmodulin-dependent enzymes. J Biol Chem 263: 15241–15244

Katsuki T, Sharpless KB (1980) The first practical method for asymmetric epoxidation. J Am Chem Soc 102: 5974–5976

Kelly SE (1991) Alkene synthesis. In: Trost BM (ed) Comprehensive oganic synthesis, vol 1. Pergamon Press, Oxford, pp 729–817

Kitamura N, Sagawa K, Takehara M (1987) Cosmetics containing α-amino fatty acids. Kokai Tokkyo Koho Jp Pat 62/4211 (January 10, 1987). Chem Abstr 106: 182464s

Krishnamurthi S, Patel Y, Kakkar V (1989) Week inhibition of protein kinase C coupled with various non-specific effects make sphingosine an unsuitable tool in platelet signal transduction studies. Biochim Biophys Acta 1010: 258–264

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 (M): 3117–3132

Kokotos G, Noula C (1996) A selective one pot conversion of carboxylic acids into alcohols. J Org Chem (accepted)

Kokotos G, Constantinou-Kokotou V, del Olmo Fernandez E, Toth I, Gibbons WA (1992) Conversion of racemic lipidic amino acids into sphingosine and ceramide analogues and 1,2-diamines. Liebigs Ann Chem: 961–964

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 (in press)

Kokotos G, Padron J-M, Noula C, Gibbons W, Martin V (1996b) A general approach to the enantiomeric synhesis of lipidic α-amino acids, peptides and vicinal amino alcohols. Tetrahedron: Asymmetry 7: 857–866

Martin VS, Woodard SS, Katsuki T, Yamada Y, Ikeda M, Sharpless KB (1981) Kinetic resolution of racemic allylic alcohols by enantioselective epoxidation. A route to substances of absolute enantiomeric purity. J Am Chem Soc 103: 6237–6240

Mori K, Funaki Y (1985) Synthesis of (4*E*,8*E*,2*S*,3*R*,2′*R*)-*N*-2′-hydroxyhexadecanoyl-9-methyl-4,8-sphingadienine, the ceramide portion of the fruiting-inducing cerebroside in a basidiomycete Schizophyllum Commune, and its (2*R*,3*S*)-isomer. Tetrahedron 41: 2369–2377

Mullmann T, Siegel M, Egan R, Billah M (1991) Sphingosine inhibits phosphatidate phosphohydrolase in human neutrophils by a protein kinase C-independent mechanism. J Biol Chem 266: 2013

Nicolaou A, Kokotos G, Constantinou-Kokotou V, York J, Gibbons WA (1995) Lipidic mimetics as inhibitors of pancreactic phospholipase A_2. Biochem Soc Trans 23: 614S

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

Roberts DC, Vellaccio F (1983) Unusual amino acids in peptide synhesis. In: Gross E, Meinhofer J (eds) The peptides, analysis, synthesis, biology, vol 5. Academic Press, New York, pp 341–449

Sagawa K, Takehara M (1987a) Polishes. Kokai Tokkyo Koho Jp Pat 62/30171 (February 9, 1987). Chem Abstr 107: 79672e

Sagawa K, Takehara M (1987b) Surface improver for ceramics. Kokai Tokkyo Koho Jp Pat 62/65964 (March 25, 1987). Chem Abstr 107: 63607b

Schollkopf U (1981) Enantioselective synthesis of (*R*)-amino acids using *L*-valine as chiral agent. Angew Chem Int Ed Engl 20: 798–799

Schollkopf U, Neubauer HJ (1982) Asymmetric synthesis via heterocyclic intermediates; XII. Enantioselective synthesis of (*R*)-α amino acids using *tert*-leucine as chiral auxiliary reagent. Synthesis: 61–864

Sweeley CC (1989) Glycosphingolipids: structure and function. Pure Appl Chem: 1307–1312

Takino H, Sagawa K, Kitamura N, Kilahara M (1987) Lubricants containing α-amino fatty acids. Kokai Tokkyo Koho Jp Pat 62/151495 (July 6, 1987). Chem Abstr 107: 220318c

Tam JP (1988) Synthetic peptide vaccine design: synthesis and properties of a high-density multiple antigenic peptide system. Proc Natl Acad Sci USA 85: 5409–5413

Tam JP (1989) Vaccine engineering: enhancement of immunogenicity of synthetic peptide vaccines related to hepatitis in chemically defined models consisting of T- and B- cell epitopes. Proc Natl Acad Sci USA 86: 9084–9088

Tietze LF, Beifuss U (1991) The Knoevenagel reaction. In: Trost BM (ed) Comprehensive organic synthesis, vol 2. Pergamon Press, Oxford, pp 341–394

Toth I (1994) A novel chemical approach to drug delivery: lipidic amino acid conjugates. J Drug Targeting 2: 217–239

Toth I, Gibbons WA (1992) Surfactants in lipid chemistry: recent synthetic, physical and biodegradative studies. The Royal Society of Chemistry, Cambridge, p 78

Toth I, Gibbons WA (1993) Peptide compounds. Brit Pat Appl GB 92157809 (July 23, 1993).

Toth I, Danton M, Flinn N, Gibbons WA (1993) A combined adjuvant and carrier system for enchancing synthetic peptides immunogenicity utilising lipidic amino acids. Tetrahedron Lett 34: 3925–3928

Toth I, Christodoulou M, Bankowsky, Flinn N, Gibbons WA, Godeau G, Moczar E, Hornebeck W (1995) Design of potent lipophilic-peptide inhibitors of human elastase: *in vitro* and *in vivo* studies. Int J Pharm 125: 117–122

Williams RM (1989) Synthesis of optically active α-amino acids. Pergamon Press, Oxford

Williams RM, Zhai W (1988) Versatile, stereocontrolled, asymmetric synthesis of E-vinyl glycine derivatives. Tetrahedron 44: 5425–5430

Zhai D, Zhai W, Williams R (1988) Alkynylation of mixed acetals with organotin acetylides. J Am Chem Soc 110: 2501–2505

Authors' address: Dr. G. Kokotos, Laboratory of Organic Chemistry, Department of Chemistry, University of Athens, Panepistimiopolis, GR-15771 Athens, Greece.

Received February 5, 1996