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Synthesis of optically active lipidic α-amino acids and lipidic 2-amino alcohols

Review Article

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Summary. Lipidic α-amino acids (LAAs) are a class of compounds combining structural features of amino acids with those of fatty acids. They are non-natural α-amino acids with saturated or unsaturated long aliphatic side chains. Synthetic approaches to optically active LAAs and lipidic 2-amino alcohols (LAALs) are summarized in this review. A general approach to enantioselective synthesis of saturated LAAs 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. Unsaturated LAAs are prepared in their enantiomeric forms by Wittig reaction *via* methyl (*S*)-2-di-*tert*-butoxycarbonylamino-5-oxo-pentanoate. This key intermediate aldehyde is obtained by selective reduction of dimethyl *N*,*N*-di-Boc glutamate with DIBAL. (*R*) or (*S*) LAALs may be prepared starting from D-mannitol or L-serine. LAAs are converted into LAALs by chemoselective reduction of their fluorides using sodium borohydride with retention of optical purity. Replacement of the hydroxyl group of LAALs by the azido group, followed by selective reduction leads to unsaturated optically active lipidic 1,2-diamines.

Keywords: Lipidic α-amino acids – Lipidic amino alcohols – Lipidic diamines – Enantioselective synthesis – Enantiomeric excess – Wittig reaction – Glutamic acid semialdehyde

Abbreviations: Bn, benzyl; Boc, *tert*-butoxycarbonyl; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; DET, diethyl tartrate; DIBAL, diisobutyl aluminum hydride; DMAP, 4-dimethylaminopyridine; DMF, *N*,*N*-dimethylformamide; DMSO, dimethyl sulfoxide; EDC, *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide; Et_3N, triethylamine; HMPA, hexamethylphosphoramide; HOBt, 1-hydroxybenzotriazole; $KN(TMS)_2$,

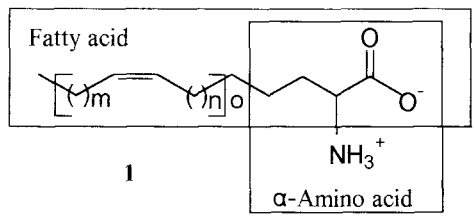
potassium bis(trimethylsilyl)-amide; LAA, lipidic α-amino acid; LAAL, lipidic 2-amino alcohol; LDA, lipidic 1,2-diamine; LP, lipidic peptide; MPM-Cl, *p*-methoxybenzyl chloride; MsCl, methanesulphonyl chloride; MTPA, α-methoxy-α-(trifluoromethyl)phenylacetic; PLA_2, phospholipase A_2; TBHP, *tert*-butyl hydroperoxide; THF, tetrahydrofuran; TMSCl, trimethylsilyl chloride; Tr, trityl; Z, benzyloxycarbonyl.

Introduction

In recent years particular attention has been focused on fatty acids and their involvement in cellular functions (Sumida et al., 1993; Horrobin, 1995). There are two types of essential fatty acids, derived from linoleic acid (n-6 or ω-6) and from α-linolenic acid (n-3 or ω-3) respectively. Neither parent essential fatty acid can be synthesized within the body and both must be provided in the diet. The essential fatty acids are constituents of cell membrane phospholipids exhibiting the following major roles: a) they determine many of the physical properties of cell membranes, b) they modulate the conformation of all membrane-associated proteins, such as ion channels, receptors, ATPases and protein kinases, c) they influence directly or indirectly almost every second messenger system which controls cell function. For example, arachidonic acid acts both as a modulator and messenger, particularly of signals triggered at the level of cell membranes.

The lipidic α-amino acids (LAAs) are a class of compounds combining structural features of amino acids with those of fatty acids. They 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, which up to six *cis* (or *trans*) double bonds may be present. LAAs, their derivatives and lipidic peptides (LPs) 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, hetero-peptides containing coded amino acids or substituted lipidic amino acids and cyclic liposome-like structures. The interesting biological properties and the various applications of LAAs and their derivatives have been presented in a review article (Kokotos et al., 1996b).

The aim of this review is to summarize the methods for the synthesis of optically active LAAs and lipidic 2-amino alcohols (LAALs).



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Scheme 1. Lipidic α-amino acid

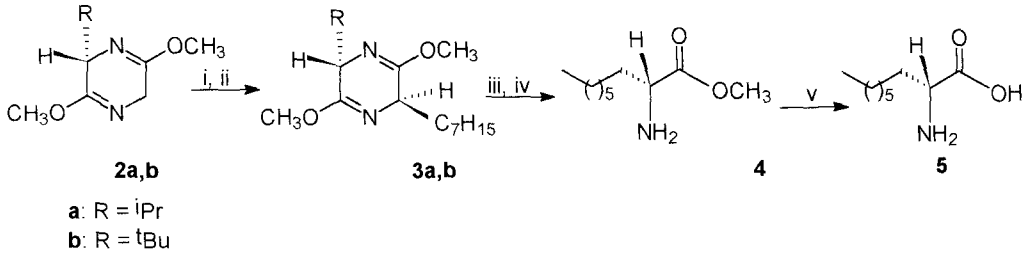
Synthesis of optically active lipidic amino acids (LAAs)

Racemic LAAs can be prepared by classical methods and resolved by chemical (Gibbons et al., 1990) or enzymatic methods (Birnbaum et al., 1953; Mori and Fukani, 1985). The interesting properties of LAAs led to the development of methods for their asymmetric synthesis.

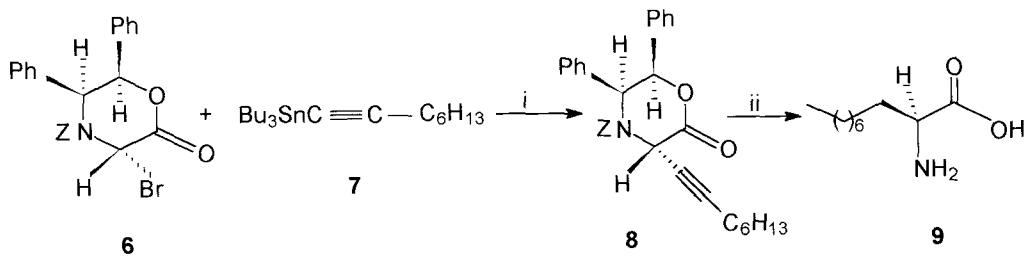
Methods to synthesize α-amino acids in optically active form have been reviewed by Williams and Duthaler (Williams, 1989; Duthaler, 1994). Some of them have been used for the synthesis of medium chain LAAs. The synthesis of (*R*)-2-aminononanoic acid **5** is based on the reaction of heptyl bromide with the lithiated bislactim ether either of cyclo(*L*-Val-Gly) **2a** (e.e 75–80%) (Schöllkopf, 1981; Schöllkopf et al., 1981) or of cyclo(*L*-*tert*-Leu-Gly) **2b** (e.e. >95%) (Scheme 2) (Schöllkopf and Neubauer, 1982).

Williams has reported the synthesis of (*S*)-2-amino-decanoic acid **9** (e.e. 98%) by the reaction of tri-n-butyltin acetylide **7** with the bromoglycinate **6** and subsequent catalytic hydrogenation (Scheme 3) (Zhai et al., 1988; Williams and Zhai, 1988).

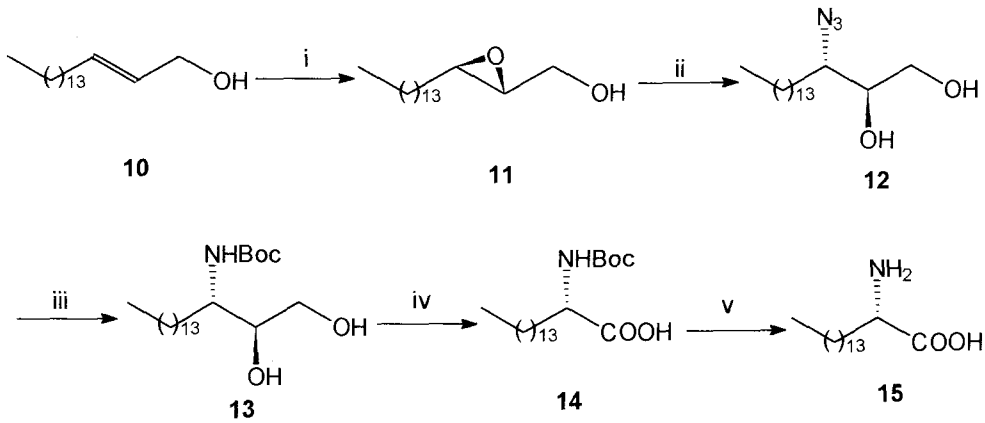
A general approach to the enantioselective synthesis of LAAs is based on the regioselective opening of chiral long chain 2,3-epoxy alcohols (Scheme 4) (Kokotos et al., 1996a). Long chain allylic alcohols may be prepared starting from either propargyl alcohol or a suitable aldehyde. Allylic alcohol **10** was submitted to Sharpless epoxidation (Katsuki and Sharpless, 1980; Martin et al., 1981) (Scheme 4) and gave epoxide **11** in high yield and enantiomeric excess (>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. Epoxide **11** opening



Scheme 2. *i* BuLi; *ii* $C_7H_{15}Br$; *iii* 0.25 N HCl; *iv* NH_3, H_2O; *v* 6N HCl



Scheme 3. *i* $ZnCl_2$; *ii* H_2, $PdCl_2$, 20 psi



Scheme 4. *i* $Ti(O\text{-}iPr)_4$, (*S*,*S*)-(−)-DET, TBHP, CH_2Cl_2; *ii* NaN_3, NH_4Cl, MeOH, H_2O; *iii* H_2, $Pd(OH)_2$, $(Boc)_2O$; *iv* $KMnO_4$, $NaIO_4$, dioxane, H_2O; *v* HCl/THF

using sodium azide and ammonium chloride yielded azido diol **12** with good regioselectivity (>10:1) and yield. *N*-Boc protected amino diol **13** was obtained by simultaneous reduction of the azido group and *N*-Boc protection.

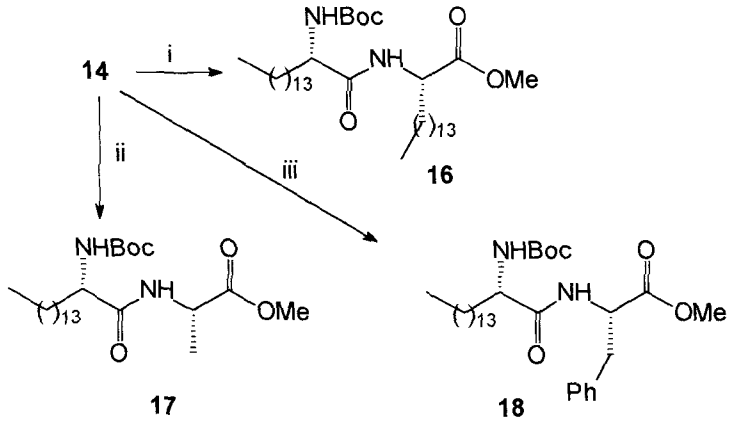
N-Boc protected amino acid **14** was produced in high yield (>85%) when 3-(*N*-*tert*-butoxycarbonylamino)-1,2-diol **13** was submitted to oxidative cleavage using potassium permanganate (Scheme 4). Final deprotection of Boc group using HCl in THF yielded the chiral LAA **15**. LAA **14** was transformed into the methyl ester, which was reduced with DIBAL in benzene at room temperature, yielding the corresponding (*S*)-2-(*tert*-butoxycarbonylamino)-hexadecanol. The preparation of the corresponding (*R*) and (*S*) Mosher esters (Dale et al., 1969) with α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA acid) and ^1H NMR analysis showed an enantiomeric excess of more than 95% (Kokotos et al., 1996a).

The lipidic dipeptide **16** and dipeptides **17**, **18** containing Ala and Phe (Scheme 5) were obtained in high yield using *N*-ethyl-*N*′-(3-dimethylaminopropyl)carbodiimide (EDC) as water soluble coupling reagent in the presence of 1-hydroxybenzotriazole (HOBt) (Kokotos et al., 1996a).

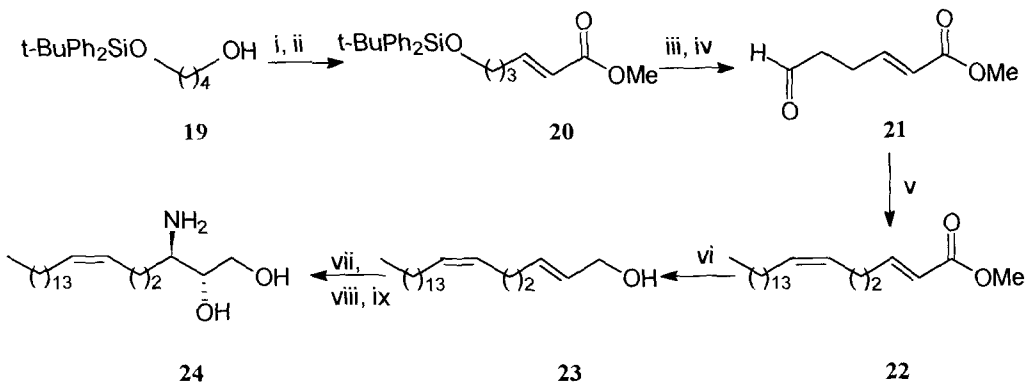
Unsaturated lipidic 3-amino-1,2-diol **24** may be obtained starting from the appropriate unsaturated allylic alcohol **23** as is outlined in Scheme 6 (Kokotos et al., 1996b). However the above mentioned methodology can not be used for the synthesis of unsaturated LAAs. It has a strong limitation, since the final step implies conditions that affect the double bonds.

An efficient and general method to prepare unsaturated LAAs in their enantiomeric forms, based on the Wittig reaction *via* methyl (*S*)-2-di-*tert*-butoxycarbonylamino-5-oxo-pentanoate, has been developed (Kokotos et al., 1998a). *L*-Glutamic and *L*-aspartic acids are very attractive starting materials for the synthesis of non-natural amino acids because they are inexpensive and may be modified selectively at the side chain carboxylic acid function after suitable protection of the α-amino group.

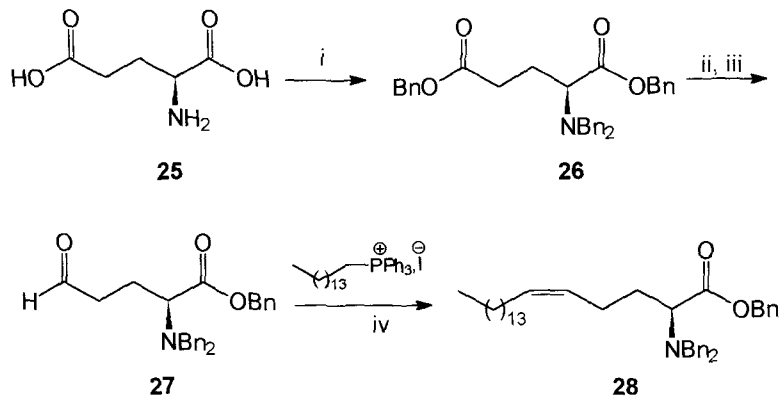
As is shown in Scheme 7 the fully protected unsaturated LAA **28** was prepared starting from glutamic acid **25**. The aldehyde **27** was obtained in high



Scheme 5. *i* EDC, HOBt, Et_3N, CH_2Cl_2, (*S*)-$CH_3(CH_2)_{13}CHNH_2COOMe$·HCl; *ii* EDC, HOBt, Et_3N, HCl·H-Ala-OMe; *iii* EDC, Et_3N, HOBt, HCl·H-Phe-OMe



Scheme 6. *i* SO_3-Pyr, DMSO, CH_2Cl_2, Et_3N; *ii* Wittig-Horner; *iii* HF, CH_3CN; *iv* SO_3-Pyr; *v* $Ph_3P^+CH_2(CH_2)_{13}CH_2,X^-$, n-BuLi, THF, HMPA; *vi* DIBAL, then H_2O; *vii* $Ti(O\text{-}iPr)_4$, (*R*,*R*)-(+)-DET, TBHP; *viii* NaN_3, NH_4Cl; *ix* $NaBH_4$, 10% Pd/C



Scheme 7. *i* BnBr, K_2CO_3, H_2O, Δ; *ii* DIBAL, ether, −78°C; *iii* H_2O; *iv* n-BuLi, THF, −78°C

yield by reduction of the perbenzylated derivative **26** with DIBAL® under controlled conditions (1.1 equiv., −78°C, 1h). The *Z*-unsaturated LAA **28** was prepared in 78% yield by the Wittig reaction of **27** with the ylide derived from pentadecyl-triphenylphosphonium iodide (*n*-BuLi, THF, −78°C). Although a wide range of conditions were employed, it was proved impossible to deprotect amino acid **28** without affecting the double bond.

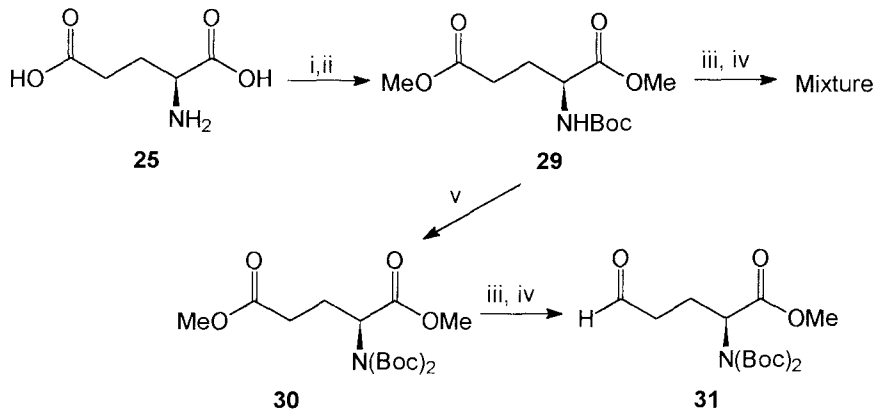
The combination of Boc and methyl ester protective groups led to satisfactory results (Kokotos et al., 1998a). Dimethyl *N*,*N*-di-Boc-glutamate **30** was reduced, using DIBAL® under controlled conditions, to give the aldehyde **31** in 85% yield (Scheme 8). It was necessary to use a second Boc group for the protection of the α-amino group, since reduction of dimethyl *N*-Boc-glutamate **29** led to a complex mixture of unidentified products.

Wittig reaction of the aldehyde **31** under usual conditions (*n*-BuLi, THF, −78°C) led to unsatisfactory results. However, when the generation of the ylide was performed with $KN(TMS)_2$, in toluene at 0°C and the Wittig reaction was performed at −78°C the *Z*-ester **32** was obtained in 92% isolated yield (Scheme 9). Compound **32** was converted into the alcohol **34**. The ^1H NMR and HPLC analysis of the corresponding (*R*)- and (*S*)-Mosher esters showed no detectable racemization.

The above described methodology opens the way for the synthesis of a wide range of unsaturated and saturated optically active α-amino acids, with almost unlimited possibilities, the only restrictions may be the synthesis of the suitable ylide and the corresponding Wittig reaction. As an application, 2-(*tert*-butoxycarbonylamino)-arachidonic acid (**36**) was prepared as illustrated in Scheme 10 (Kokotos et al., 1998a).

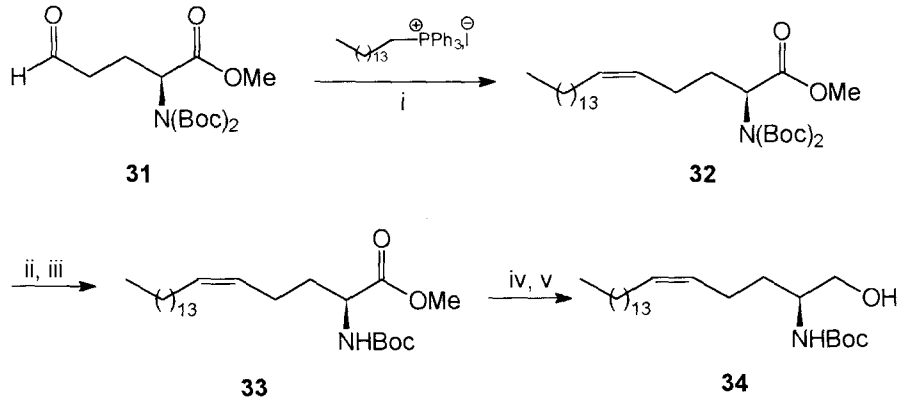
Synthesis of optically active lipidic 2-amino alcohols (LAALs)

Sphingosine and ceramide are the basic structural units of the sphingolipids which are essential membrane and cell wall constituents. A great number of

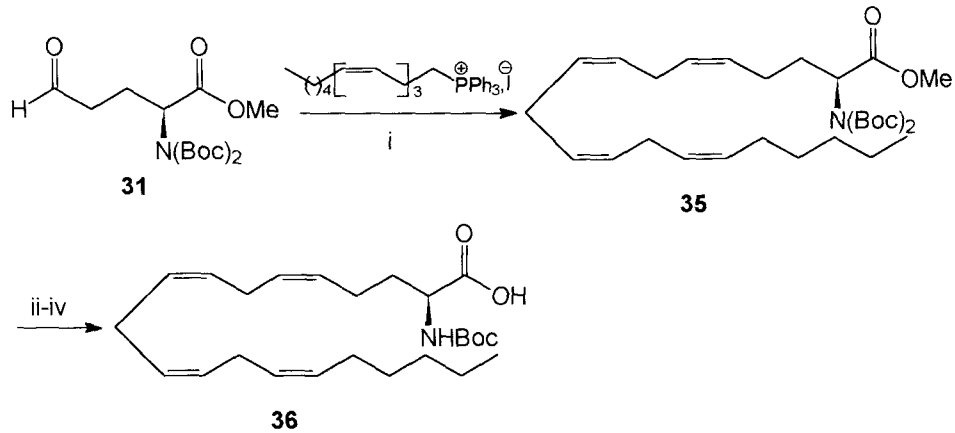


Scheme 8. *i* TMSCl, MeOH; *ii* $(Boc)_2O$, Et_3N, MeOH; *iii* DIBAL, ether −78°C; *iv* H_2O; *v* $(Boc)_2O$, DMAP, CH_3CN

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). Sphingosine modulates the activity of several enzymes involved in signal transduction and cell growth, such as phospholipase A_2 (PLA_2) and phospholipase D (Franson et al., 1992), protein kinase C (Hannun et al., 1986) and other kinases (Fiore et al., 1990; Krishnamurti et al., 1989), phosphatidate phosphohydrolase (Mullmann et al., 1991) and several calmodulin – dependent enzymes (Jefferson and Schulman, 1988). Ceramide has emerged as a candidate intracellular mediator for the action of extracellular agents (for example tumor necrosis factor) and has multiple cellular and biochemical targets. In particular, ceramide is a potent and specific suppressor of cell growth (Hannun and Obeid, 1995). Thus, structural analogues of sphingosine and ceramides present great interest for biological testing. Synthetic routes to



Scheme 9. *i* $KN(TMS)_2$, toluene, −78°C; *ii* 5N HCl, THF; *iii* $(Boc)_2O$, Et_3N, MeOH; *iv* DIBAL, C_6H_6, 0°C; *v* H_2O

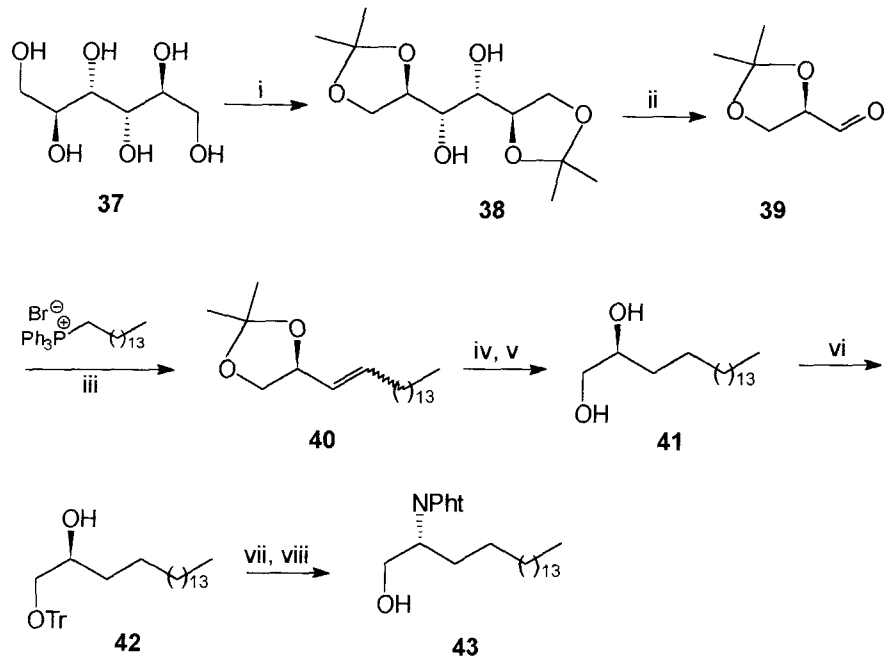


Scheme 10. *i* $KN(TMS)_2$, toluene, −78°C; *ii* 4N HCl, THF; *iii* $(Boc)_2O$, Et_3N, MeOH; *iv* NaOH, dioxane, then H^+

LAALs that are considered sphingosine analogues, have been developed and interesting biological activities for these compounds have been identified.

(*R*)- and (*S*)-2-*N*-phthalimido-octadecanol were prepared starting from (*R*)- and (*S*)-2,3-*O*-isopropylidene glyceraldehyde (Massing and Eibel, 1994). The synthesis of (*R*)-2-amino-octadecanol (**43**) is illustrated in Scheme 11. D-mannitol (**37**) was selectively protected as acetonide at 1,2- and 5,6-diol groups and the C3–C4 bond of **38** was cleaved by sodium metaperiodate. Wittig reaction with the aldehyde **39** using pentadecyl triphenylphosphonium bromide, followed by hydrogenation and removal of the isopropylidene group yielded 1,2-octadecanediol **41**. Selective protection of the primary hydroxyl group was possible by tritylation. The free hydroxyl group of **42** was converted into phthalimido group with complete inversion of the configuration using Mitsunobu reaction. (*R*)- and (*S*)-**43** were used for the synthesis of enantiomerically pure 1-*O*-phosphocholine-2-*N*-acyl octadecane (Massig and Eibl, 1994).

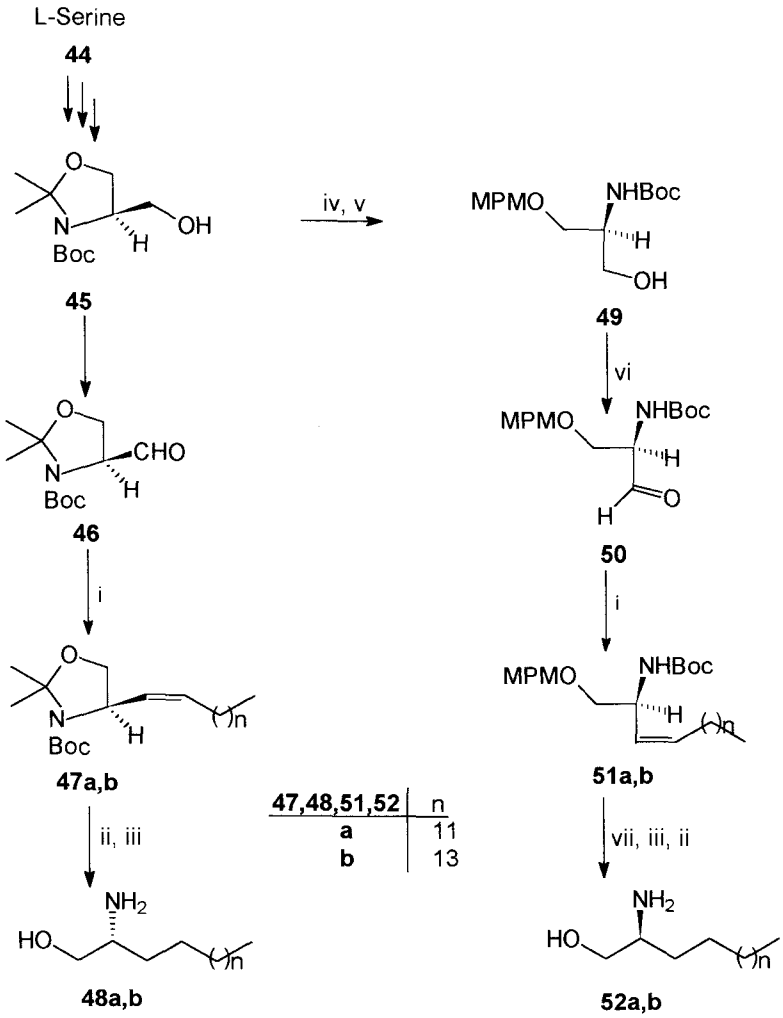
(*R*)- and (*S*)-2-amino-hexadecanol and eicosanol were synthesized starting from *L*-serine (**44**) (Hirose et al., 1996). (Scheme 12). The key intermediate aldehyde **46** (Garner and Park, 1987; Garner and Park, 1992) was submitted to Wittig reaction. Removal of the protective groups of **47a,b** followed by hydrogenation, gave (*R*) enantiomers **48**. Treatment of **45** with p-methoxybenzyl chloride in the presence of NaH, followed by deprotection of the acetonide, afforded the reverse-configurated alcohol **49**. Compound **49** was oxidized to give the aldehyde **50** and converted into the olefines **51a,b**. Hydrogenation



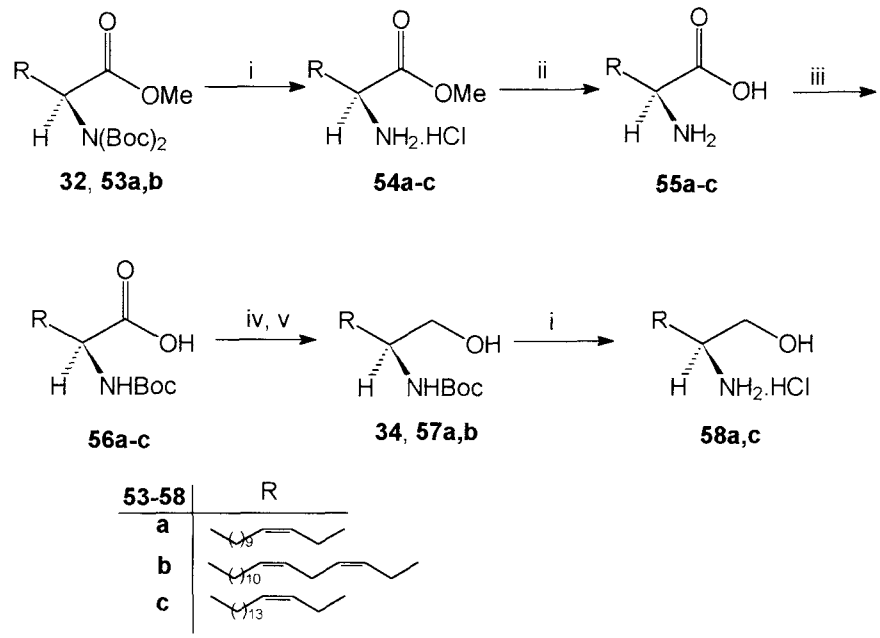
Scheme 11. *i* CH_3COCH_3, $ZnCl_2$; *ii* $NaIO_4$, H_2O, pH = 7.0; *iii* n-BuLi, THF, −78°C; *iv* H_2, 10% Pd/C, pH = 7.0; *v* 2N HCl, 50°C; *vi* TrCl, Et_3N, toluene, Δ; *vii* PPh_3, phthalimide, diethylazodicarboxylate; *viii* H_2SO_4, dioxane, MeOH, 50°C

and removal of the protective groups led to (*S*) enantiomers **52**. A series of optically active LAALs were tested as immunosuppresants (Hirose et al., 1996). The (*R*)-enantiomers were more potent than the (*S*)-enantiomers and (*R*)-2-aminohexadecanol **48a** displayed comparable activity to the potent immunosuppresant FTY720 (Adachi et al., 1995).

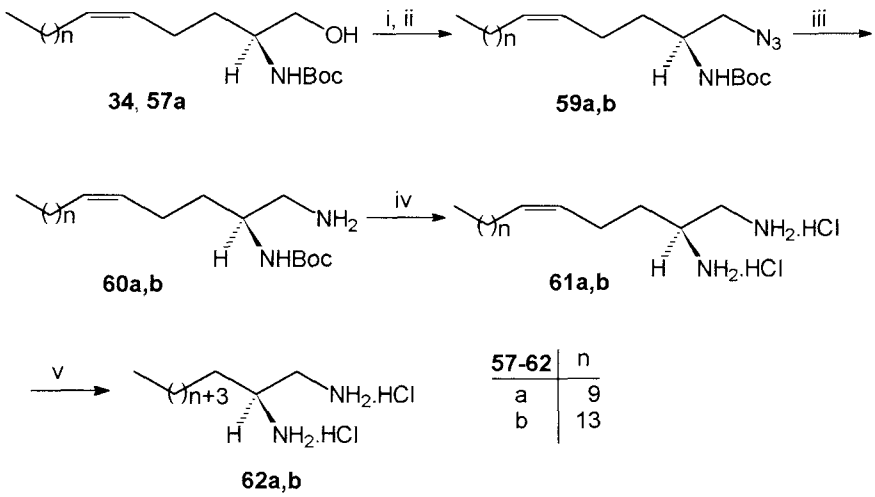
Unsaturated LAALs can be prepared in their enantiomeric forms starting from unsaturated LAAs, synthesized by the general method described in Scheme 9. Free LAAs **55a–c** were obtained from **32**, **53a,b** by treatment with HCl/THF, followed by saponification (Markidis et al., 1997) (Scheme 13). It has to be noticed that direct saponification of **32**, **53a,b** was incomplete even after 48h and resulted in considerable racemization. Boc-protected LAAs **56a–c** were converted into alcohols **34**, **57a,b** by chemoselective reduction of their fluorides (Kokotos and Noula, 1996). Acyl fluorides were prepared by treatment with cyanuric fluoride in the presence of pyridine and were reduced



Scheme 12. *i* $Ph_3P^+C_{n+2}H_{2n+5},Br^-$, $KN(TMS)_2$; *ii* 4N HCl; *iii* H_2, 10% Pd/C; *iv* MPM-Cl, NaH; *v* 90% AcOH aq, LiCl; *vi* SO_3-pyr, Et_3N; *vii* DDQ



Scheme 13. *i* 5N HCl/THF; *ii* MeOH, NaOH 1N; *iii* $(Boc)_2O$, Et_3N, MeOH; *iv* cyanuric fluoride, pyridine, CH_2Cl_2; *v* $NaBH_4$, MeOH



Scheme 14. *i* MsCl, Et_3N, CH_2Cl_2; *ii* NaN_3, DMF; *iii* THF, $NaBH_4$, 10% Pd/C, MeOH; *iv* 5N HCl/THF; *v* H_2, 10% Pd/C

in situ to primary alcohols by sodium borohydride with dropwise addition of methanol. This method for reduction is compatible with double bonds and proceeds with retention of optical purity. Sphingosine analogues **58a,c** were obtained by removal of Boc groups of **34** and **57a**.

Unsaturated LAALs were converted into chiral lipidic 1,2-diamines (LDAs) as described in Scheme 14 (Markidis et al., 1997). The hydroxy group

of **34**, **57a** was activated by conversion to mesylate and the methanesulphonyloxy group was replaced by the azido group. The selective reduction of the azido group of **59a,b** was carried out using sodium borohydride in the presence of 10% Pd/C in a mixture of tetrahydrofuran-methanol. Free LDAs **61a,b** were obtained by removal of the protecting group and were converted into saturated derivatives **62a,b** by catalytic hydrogenation.

Racemic LAALs and LDAs were found to inhibit PLA_2 in a bulk radiometric assay (Noula et al., 1996). However, these molecules seemed to cause indirect "inhibition" modifying the "interfacial quality". Moreover, LAALs and LDAs inhibit the carrageenin-induced paw edema in rats (Kokotos et al., 1997). 1,2-LDAs exhibited the highest *in vivo* anti-inflammatory activity, while the optical purity did not seem to influence the activity. On the other hand, racemic 1,2-hexadecanediamine has been proved to present potent *in vitro* cytotoxic activity against various cell lines (Kokotos et al., 1998b).

Acknowledgments

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