STUDIES TOWARDS THE SYNTHESIS OF PHOSPHATIDYLCHOLINE ANALOGUES

M.Sc. **1995** **F. DEMIRCI**

Studies towards the synthesis of phosphatidylcholine analogues

A thesis submitted by **Fatih Demirci** in part fulfilment of the requirements for the degree of Master of Science by research at the University of East Anglia.

March 1995

Declaration

The research described in this thesis has been performed at the University of East Anglia, School of Chemical Sciences, under the supervision of ***Dr. Alan H. Haines****, funded by the Turkish Government, Anadolu University, Faculty of Pharmacy and is, to the best of my knowledge, original except where due reference is made to other authors.*

Fatih Demirci

“to my family”

“sonsuz sevgimle, ailem için...”

“Hafıza-î beşer nisyân ile malûldür”

Acknowledgements

First of all I would like to thank my supervisor ***Dr. Alan H. Haines*** *who opened a big window for me into the chemistry world, and supported me in all matters throughout my MSc study period.*

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Finally I would like to express my very special thanks to my family, for giving me strength.

Abstract

A new synthetic route towards the compound 2,3-diaminopropan-1-ol **2** was developed in order to provide the starting material for the synthesis of diamido analogues of phosphatidylcholine which show potential as anti-HIV agents. The diamino alcohol **2** was synthesised in both racemic and a chiral form starting from the amino acid and chiral building block serine. Serine was used as the readily available methyl ester hydrochloride in racemic form **18** ·HCl or as the L-enantiomer **18c** ·HCl.

Syntheses were investigated with a variety of different protecting groups, for example *t*-butyloxycarbonyl or benzyloxycarbonyl for *N*-protection coupled with *N, O*-protection by the isopropylidene group to give oxazolidine derivatives. As an alternative strategy, *N, O*-protection was achieved by reaction of **18** ·HCl and **18c** ·HCl with ethyl benzimidate to give 4,5-dihydrooxazole derivatives. The successful conversion of the ester group into the aminomethyl group was achieved with the oxazolidine derivatives in several steps to give, after removal of protecting groups, the required diamino alcohol **2**, in both racemic and one chiral form.

Abbreviations

AIDS	: acquired immune deficiency syndrome
Ar	: aromatic
Boc	: *t*-butyloxycarbonyl
Bn	: benzyl
Cbz	: benzyloxycarbonyl
DMAP	: 4-(dimethylamino)pyridine
DMF	: *N,N*-dimethylformamide
DMP	: 2,2-dimethoxypropane
DNA	: deoxyribonucleic acid
Et	: ethyl
HIV	: human immunodeficiency virus
Hz	: hertz
$LiAlH_4$	: lithium aluminum hydride
IR	: infrared
M	: molar
Me	: methyl
m.p.	: melting point
NMR	: nuclear magnetic resonance
Ph	: phenyl
PTSA	: *p*-toluenesulfonic acid
R_f	: retention factor
RNA	: ribonucleic acid
THF	: tetrahydrofuran
TLC	: thin layer chromatography
TMS	: tetramethylsilane
Ts	: tosyl

Contents

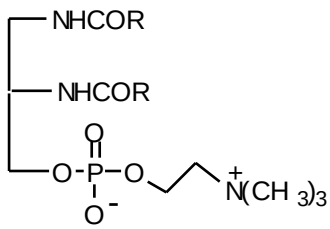
CHAPTER 1

INTRODUCTION

1. INTRODUCTION

1.1. General Aims of Project and Contents of Chapter

The main aim of the work presented in this thesis was to develop a new synthesis of phosphorylcholine derivatives of 2,3-diacylamidopropan-1-ol, general structure shown in **1**, compounds which are analogues of phosphatidylcholine and which form a class of compounds with potential for anti-HIV activity.¶ In particular we wished to investigate synthetic routes which would afford each of these materials in their enantiomeric forms. The amino acids DL-serine and L-serine were used as starting materials to synthesise the key intermediate 2,3-diaminopropan-1-ol **2**, in racemic form and in one of its chiral forms, respectively.



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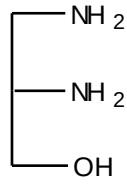

2

In this introductory chapter is given a brief description and overview of Acquired Immune Deficiency Syndrome (AIDS) and the effects on this disease of phosphatidylcholine type analogues, some general aspects of the use of natural products in asymmetric synthesis, and the use of the amino acid serine and its derivatives in synthesis.

¶ In this thesis, the Fischer projection formulae are not intended to specify absolute configurations, unless stated specifically.

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1.2. AIDS and Phosphatidylcholine Analogues in Context

Acquired Immune Deficiency Syndrome (AIDS) is the worst human plague since the "black death" of the middle ages. This annihilating disease was first described by different researchers in 1981¶ and it is the final stage of infection by the Human Immunodeficiency Virus (HIV) identified in 1983 by Barré-Sinoussi and co-workers.[2] HIV is a retrovirus in which the genetic information is stored as RNA rather than DNA. As with all viruses, retroviruses replicate by modifying the biochemical machinery of the host cell in order to produce further copies of the virus. Most importantly, however, with retroviruses, the ordinary flow of the genetic information is reversed and the viral RNA is first transcribed into DNA, which is then incorporated into the host DNA. One of the key viral enzymes is reverse transcriptase, which uses viral RNA as a template for producing the complementary DNA which is than incorporated by means of another enzyme (integrase) into the host DNA. When the copying process begins, the modified host DNA is transcribed back into RNA and this is translated into virus-specific proteins which self-assemble into new copies of the retrovirus. The epidemiological evidence investigated in different countries indicated that, in all patients with AIDS, HIV was present. HIV infects and destroys T4 lymphocytes[3] which have a vital importance in the immune response and confer cell-mediated immunity. The main T4 lymphocytes are responsible, amongst other functions for long term protection against some viruses, bacteria and malignant cells.[4] In the case of AIDS, the huge loss of T4 lymphocytes is responsible for the breakdown of the immune system.[5,6]

Infection by HIV is brought about by sexual contact, blood transfusion or organ transplants. However, a person with the HIV virus may stay healthy for a period from

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¶ Early investigations are summarised in an article by the key researchers Gallo and Montagnier[1]

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months up to several years without showing any significant symptoms of AIDS, except for the virus present in the lymphocytes. This period is called the latent and prodromal stage, but once the virus becomes active and the immune system becomes weaker, fatal illnesses are unavoidable. Later stages of opportunistic infections and tumours (lymphomas and Kaposi's sarcoma) may last for 1-2 years before resulting in the patient's death.[7]

The main identified and described AIDS-associated sites and diseases, among many others, are the brain (with tumours and inflammation), the respiratory system (with *Candidiasis* on the upper regions, *Pneumo carinii* infection, fungal infections and tuberculosis), the intestines (with protozoal and especially *Salmonella* infections), and the skin (mainly with Kaposi' s sarcoma, fungal infections and Herpes zoster virus).[6,7]

A simple illustration of the cellular mechanism of the HIV infection is shown in **Fig.1**.[7] The basic cycle is that the virus binds to the receptor, enters the cell (T4 lymphocyte) and, after unfolding of the protein coat and liberation of the viral constituents, the enzyme reverse transcriptase replicates the virus RNA producing a complementary DNA copy.

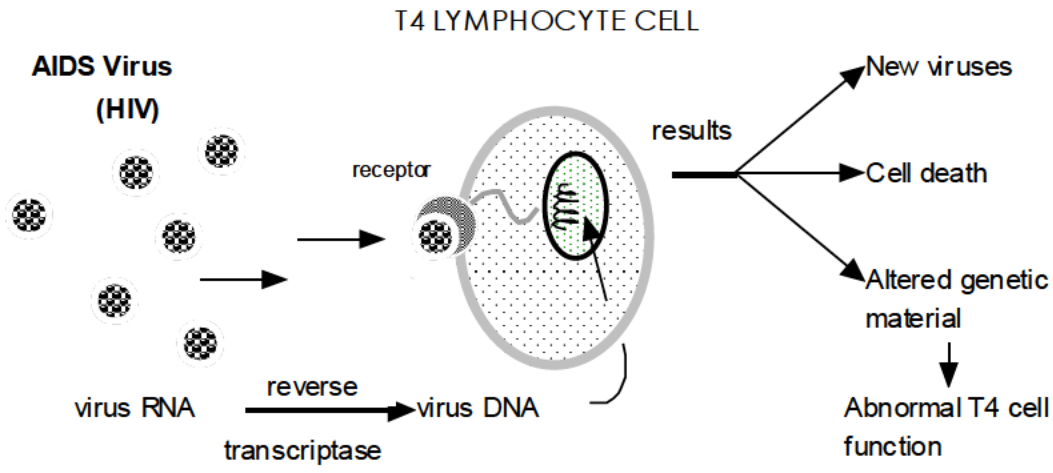

Fig.1 Replicative Cycle of HIV

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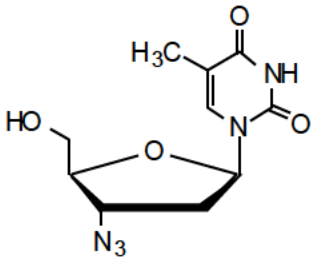
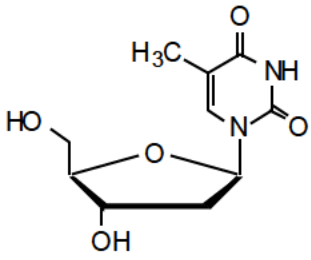
The transcribed viral DNA is incorporated into the cell DNA through the action of another viral enzyme, integrase. After the translation into virus proteins and assembly, new viruses burst from the cell usually resulting in death of the T4 cell. If the cell survives it does so with the modified DNA resulting in abnormalities.

WHO global AIDS statistics, as reported at 30 June 1994, showed that 985,119 people were suffering from AIDS whereas over 16 million infections with HIV were estimated.[8] The reasons for AIDS being epidemic and dangerous are more due to social factors than because of its high infectivity. Blood transfusions and organ transplants are also important factors for spreading the disease.[9]

Due to the complex structure of the HIV and its ability to undergo rapid genetic change, it has not yet been possible to discover a therapeutic agent against the virus. However, the National Cancer Institute in the United States screened an active compound, 3'-azido-3'-deoxythymidine (AZT) **3**, which proved promising and is still one of the most effective drugs given to AIDS patients.[3,10]



3'-azido-3'-deoxythymidine (AZT) **3**



thymidine **4**

AZT was given for the first time in 1985 to HIV-infected patients and led to a significant improvement both in the survival period and the quality of life of patients. The compound was thought to exert its effect by inhibiting the enzyme reverse transcriptase and by acting as a DNA chain terminator; it should be noted that AZT lacks the required 3'-OH group present in the normal 2'-deoxy nucleoside thymidine **4**. Some 2',3'-dideoxy nucleosides such as 2',3'-

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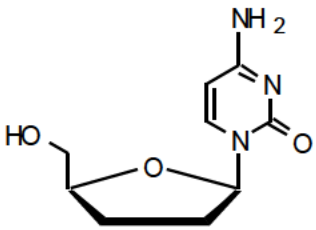
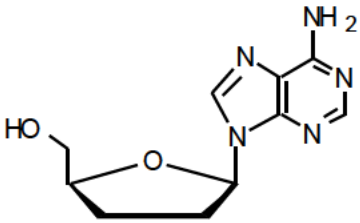
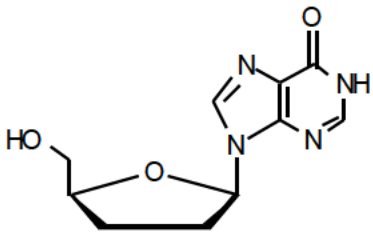
dideoxycytidine (ddC) **5**, 2',3'-dideoxyadenosine (ddA) **6**, and 2',3'-dideoxyinosine (ddI) **7** act also as chain terminators in nucleic acid synthesis by replacing the usual 2'-deoxynucleotides in the growing DNA chain and thus prevent the replication of HIV. A more recent development in this area is the compound 2',3'-dideoxy-2',3'-didehydrothymidine (D_4T) **8** which acts in similar manner to bring about chain termination. Although AZT, ddC, ddI and D_4T are to date the only nucleoside based drugs for the clinical treatment of AIDS, they have severe disadvantages, especially toxic side effects.[10,11]



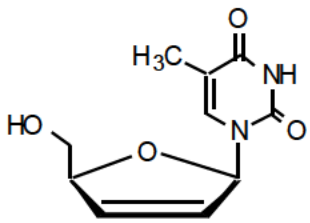
ddC **5**



ddA **6**



ddI **7**



D_4T **8**

Several other agents have shown promise for AIDS chemotherapy but none has proved to be a cure for the disease. Thus, compounds which inhibit HIV protease, essential for viral replication, have been prepared and tested, for example compound **9** which was developed by Roche[12] and given the descriptor RO 31- 8959. This is a novel potent and selective inhibitor of the protease. More recently Bennett and co-workers[13] developed a new methodology to synthesise compound **9** and derivatives in the form of diastereoisomers for further investigations.

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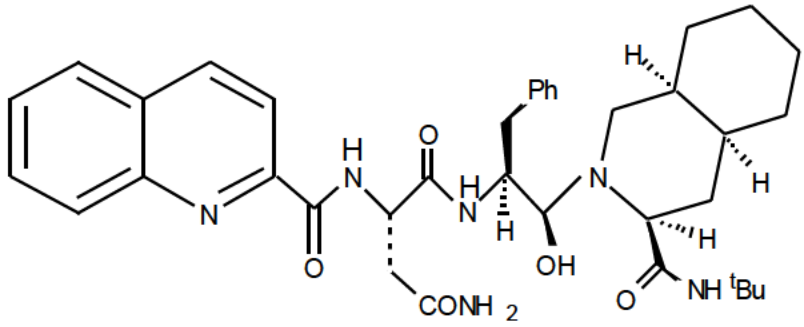
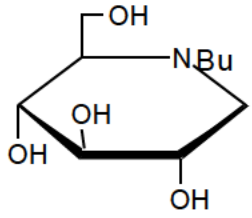


RO 31- 8959 **9**

Other compounds which inhibit trimming glycosidases, such as 1-deoxynojirimycin and castanospermine, show anti-HIV activity[14] and one such compound, *N*-butyl-1-deoxynojirimycin **10**, was subject to clinical trials,[15] although the results from this study have not been published. Various glycosidases are of vital importance to the modification of the glycoprotein which forms the coat of the virus, and their inhibition leads to virions with lowered infectivity and can also inhibit replication of the virus.[10]



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Work to try and identify the important structural features in 1-deoxynojirimycin which are responsible for the anti-HIV activity has involved the synthesis of the acylic analogues which were the subject of another project in our research group.[16,17]

Since there is no present therapy for AIDS, prevention appears to be of primary importance in order to prevent the spread of the disease. The 10th International Conference on AIDS which took place in August 1994 at Yokohama, confirmed that currently prevention of infection is the only reliable way to attack HIV.[18] In addition to prevention, education and long term planning and strategy will be very important in the control and treatment of AIDS in the future.

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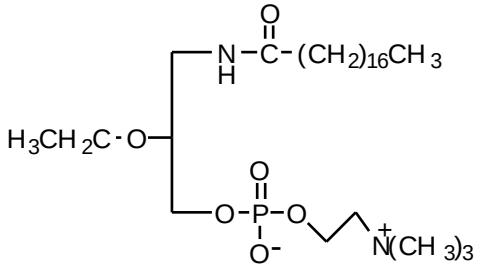
Many classes of compound have been examined in the hope to find lead compounds for new anti-HIV drugs and amongst these are some phosphatidylcholine analogues. Thus Piantadosi and co-workers[19] reported that a variety of synthetic glycerol lipids substituted with thio, oxy or amidoalkyl functionality and either a phosphocholine or quaternary ammonium moiety, possessed some anti-HIV activity. The most promising compound was the 1-octadecanamido-2-ethoxypropylphosphocholine **11**. Mechanistic studies indicate that these compounds are not reverse transcriptase inhibitors but that they appear to inhibit a late step in HIV replication. The possible mechanism of action could be explained by the membrane-interactive property of phospholipids which could cause fluidization of cell membranes in a similar manner to that suggested for cancer cell membranes.[20] Combination-therapy studies with AZT show synergistic effects in inhibiting HIV replication.



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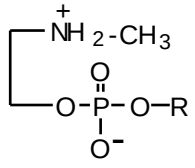
It is also known that modified phospholipids are anti-cancer agents, particularly lyso phospholipids.[21]

In work related to that of Piantadosi,[19] McGuigan and co-workers[22] discovered new and very simple alkyl phosphatidyl *N*-methyl ethanolamines, for example **12,** that have selective anti-HIV activity.



R= oleyl

12

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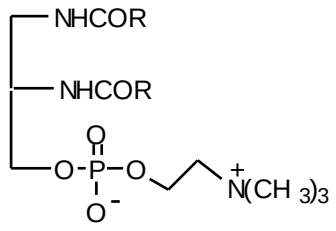
Previous work[23] in our research group into the synthesis and testing of diamide analogues of phosphatidylcholine (racemic forms), having the general formula **1**, had indicated that these compounds (especially compound R= $(CH_2)_{10}Me$) possess moderate anti-HIV activity. The synthesis of **1** required the preparation of 2,3-diaminopropan-1-ol **2**, and further investigation of this series of compounds required the development of a more convenient synthesis of this alcohol and also the preparation of both enantiomeric forms of this compound. The study of these syntheses forms the major part of this thesis. These compounds are nitrogen analogues of the naturally occurring phosphatidylcholine **13** (absolute configuration as shown) which has long been known.



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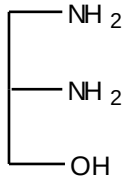

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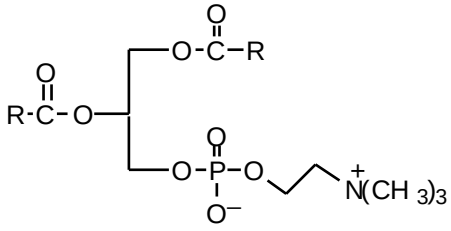

13

A phosphorus-containing lipid, which we know as phosphatidylcholine or lecithin, was discovered by Vanquelin in 1811 who extracted it from the brain tissue. Gobley also isolated the compound, from egg-yolk and brain tissue, and he later named the compound "lecithin" (from the Greek ‘lekitos’, meaning egg-yolk) in 1850. Later in 1862 Strecker was able to isolate lecithin from hog bile and with Diaconow he deduced the structure of the compound. Further studies by Strecker stated that the choline was attached to the phosphate by an ester linkage. This early work has been summarised.[24]

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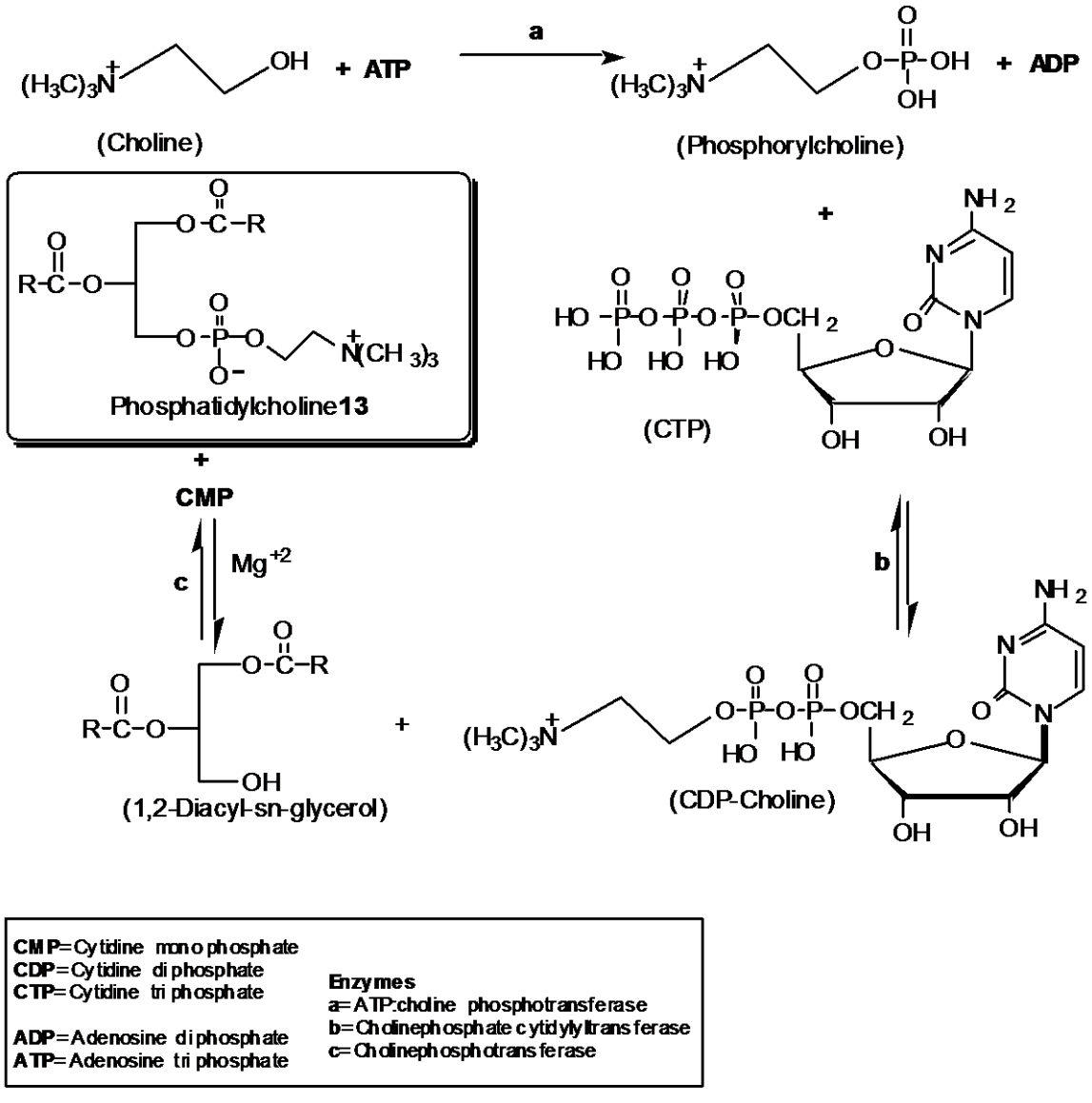
Phosphatidylcholine is the main phosphorus-containing lipid of most animal tissues. Its biosynthesis[25] was investigated originally by Kennedy and Weiss. In mammals, phosphatidylcholine is produced in the liver by methylation of phosphatidylethanolamine by *S*-adenosylmethionine, but in all other tissues it is produced only by a reaction between 1,2-diacylglycerol and CDP-choline.[24] The latter biosynthetic pathway is given in **Scheme 1**.



Scheme 1 Phosphatidylcholine biosynthesis

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Phosphatidylcholines are of commercial interest,[26] and there is an increasing demand for phospholipids and their derivatives. It is well known that phospholipids are main constituents of biological membranes and also take part in certain cellular transportations. This feature makes them important in liposome technology as carrier molecules. Phosphatidylcholines are used in the preparation of liposomes which have potential as drug delivery systems. Liposomes from synthetic phospholipids are ideal carriers for drugs since the carrier material is of biological origin, but well defined in structure and configuration, which makes them interesting to the pharmaceutical industry for preparing targeted drugs for various diseases.

1.3. Natural Products and Asymmetric Synthesis

In general terms natural products can be defined as the products of primary or secondary metabolism. Primary metabolites are vital and essential for the organism whereas secondary metabolites are restricted in occurrence and apparently have no useful role.[27]

Most natural products are optically active and their biological activity is usually associated with only one enantiomeric form. Thus, in general, the receptor sites in biological systems recognise just one of the two possible enantiomers. It is possible that the other enantiomer has unrequired biological activity. The drug Thalidomide is a good example of such a case. The *R*-enantiomer has the desired sedative effect, whereas the *S*-enantiomer has a teratogenic effect. After introduction of this drug in 1963, many cases of foetal deformities were reported as a result of its use during pregnancy. Optically active compounds are now synthesised in their enantiomerically pure form, and clinical tests are conducted on both enantiomers. As indicated in an important review of asymmetric synthesis in 1989,[28] authorities for the pharmaceutical and agrochemical industries will insist on detailed information concerning the biological properties of individual enantiomers of all new candidate compounds. In 1982 Drauz and co-workers reported that only about 20% of optically active pharmaceuticals were then traded as pure enantiomers.[29] Clearly, the

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requirement for the synthesis of optically pure compounds has since changed dramatically. This has led to an increasing interest in stereoselective syntheses.[30]

There are two possible strategies for the synthesis of a chiral compound, in the form of a single enantiomer. The more common and frequently easiest strategy to introduce chirality is to begin with a single stereoisomer and to use a synthesis that does not affect the chiral centre.[31] Typically the starting material would be readily obtained from nature in high enantiomeric purity. Starting materials such as amino acids, amino alcohols, hydroxy acids, alkaloids and other amines, terpenes and carbohydrates are widely used for this purpose.[32]

A definition of asymmetric synthesis given by Eliel and co-authors,[33] is the synthesis of a chiral substance from an achiral precursor such that one enantiomer predominates over the other. Because of lack of agreement on how to extend the definition to substances where molecules already contain at least one chiral element and where the synthesis introduces a new chiral element, it is preferable to replace this term by stereoselective synthesis, enantioselective synthesis or diastereoselective synthesis.

Asymmetric synthesis itself has become an increasingly required technique for organic chemists and represents a considerable challenge. One of the key workers in this field is Meyers[34] who introduced asymmetric carbon-carbon bond forming reactions with chiral oxazolines. α-Amino acids are also important chiral educts for preparing compounds. Rapoport and co-workers[35] have described an interesting conversion of readily available L-α-amino acids into the D-isomers. In particular, L-serine was found to be a useful starting material. In this, context Garner and Park[36] have used serine and threonine to prepare oxazoline aldehydes (for example the Garner aldehyde **14** from serine) which are ideally suited as chiral, non-racemic synthons for the asymmetric synthesis of nitrogen containing targets.

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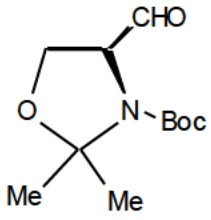
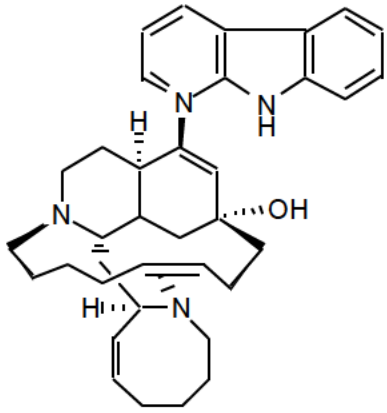


Garner's Aldehyde **14**



Manzamine A **15**

As mentioned above, there are several classes of compounds in nature readily available for asymmetric synthesis. Amongst these the amino acids are especially good starting materials. For example Pandit and co-workers[37] synthesised the natural product Manzamine A **15**, which has useful biological activity, starting from an amino acid (L-serine). New kainoids possessing neuroexcitatory activities have been synthesised in enantiomerically pure form by Benetti[38] and his research group, using the same starting material. Hassner and co-workers recently published a synthesis of asymmetric pyrrolidines from L-serine which are selective α-glucosidase inhibitors.[39] These three examples represent only a small proportion of many studies in this area. Since our own work involves the use of serine as a starting material, we give in the next section a very brief overview of its occurrence, availability and use in synthesis.

1.4. The Amino Acid Serine As Starting Material

The amino acids are the simplest units, building blocks from which the proteins are made. They are the "substances of life" and occur in every living organism. Proteins possess different structures and, depending on their structures, perform different functions. Amino acids, covalently linked together by amide bonds build the peptides or proteins which are vitally important for life. Peptides usually refer to the polyamides containing up to 50 amino

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acids, but proteins are much bigger. All twenty of the DNA encoded amino acids in nature exist in the L-enantiomeric form. Therefore, the D-enantiomers are rare and usually need to be obtained by synthesis.[27,40] Although D-amino acids do not generally occur in proteins, they are incorporated into secondary metabolites produced by some bacteria.[24]

All common amino acids which build up proteins (excluding glycine) are chiral, generally of the L-form, and they are the most widely used single class of chiral starting materials for synthesis.[41] Since the commercially available amino acids are obtained either from proteins by hydrolysis or by microbiological processes, the L-isomers are readily obtained, which explains the cost difference between the natural and unnatural enantiomers. The availability[42a,b] of serine in its racemic and enantiomeric forms is illustrated in **Fig. 2.**

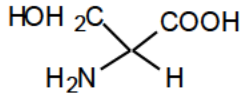
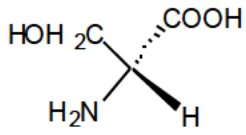
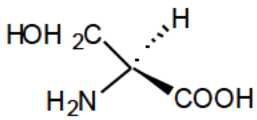
	DL-Serine[¶]	100 g approx.- £ 11.00-15.00
	D-Serine	100 g approx.- £ 120.00-140.00
	L-Serine	100 g approx.- £ 29.00-30.00

Fig. 2 Enantiomers of serine and prices

[¶] The chirality of the amino acids is usually described by the descriptor D- or L-, which has its origins in the Fischer nomenclature of the sugars. The more modern descriptors of chirality, *R*- and *S*, are also used and L-serine is equivalent to *S*-serine.

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The amino acid L-serine (2*S*)-(2–amino-3-hydroxypropionic acid) was first isolated in natural form by Cramer in 1865 from a silk protein.[43,44] Later studies and investigations by Fischer and Leuchs in 1902 established its structure and synthetic methods for its preparation.[45] L-Serine is found predominantly in proteins and also in silk fibroin. D-Serine is found in some bacteria, earthworms, and in some antibiotics, for example polymyxin.[40]

All amino acids are derived from intermediates in glycolysis, in the citric acid cycle or in the pentose phosphate pathway. Some amino acids (for example serine), have a very simple biosynthetic pathway and only a few enzymatic steps are required for conversion from their precursors. However, different organisms vary in their abilities to synthesise all of them. Whereas plants and bacteria are able to synthesise all of the amino acids usually found in nature (about 21 in number), mammals can only synthesise about half of these, which are thus not needed in the diet. The essential amino acids (for example histidine, phenylalanine, valine) must be obtained from the diet.[25] Serine need not to be included in the diet as it is a glycogenic amino acid (readily synthesised by the body).[46]

In asymmetric synthesis, amino acids with aliphatic side chains (alanine, valine) are used largely for their steric directing effects whereas other amino acids with functional groups in the side chain, particularly -OH (serine, threonine), -NH_2 (lysine, ornithine), -SH (cysteine), -COOH (aspartic, glutamic acids) allow a wide variety of applications beside the amino acid functionality.[30]

Serine is a chiral amino acid which is reasonably cheap, easily available in both enantiomeric forms, useful in its side-chain functionality and non-toxic. It is widely used as starting material for many reactions in organic synthesis, especially in chiral synthesis.[47-53]

References for Chapter 1 start on page 17

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CHAPTER 2

RESULTS AND DISCUSSION

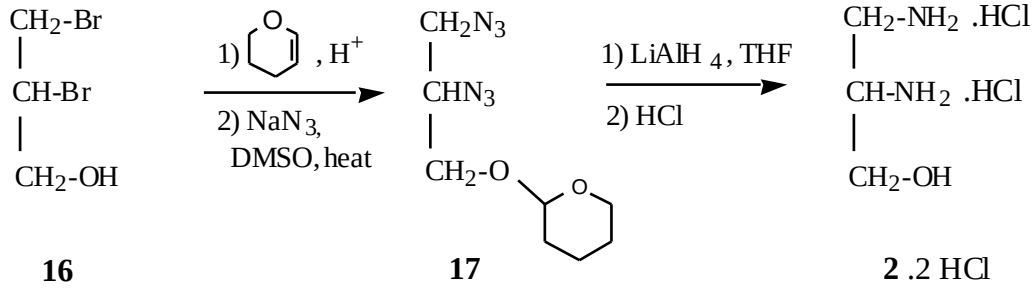
2. RESULTS AND DISCUSSION

2.1. General Overview

In Chapter 1, reasons were given for the interest in synthesising phosphatidylcholine analogues and in particular, those based on 2,3-diaminopropan-1-ol **2.** A brief survey was given on asymmetric synthesis using natural products as starting material and attention was focused on the amino acid serine as a possible starting material, for the preparation of **2**. This chapter discusses investigations into devising a simple route from the amino acid serine which would avoid the previous hazardous route via diazide chemistry, and which would afford chiral material.

2.2. Synthesis of 2,3-Diaminopropan-1-ol from 2,3-Dibromopropan-1-ol

Although 1,3-diaminopropan-2-ol is commercially available, the racemic 2,3-diaminopropan-1-ol, surprisingly, does not appear in the common chemical catalogues. The compound has been prepared from 2,3-dibromopropan-1-ol[1] (**Scheme 2**) via hydroxyl group protection, azide displacement, reduction to the diamine and finally acid



16 **17** **2** .2 HCl

Scheme 2 Previous synthesis of 2,3-diaminopropan-1-ol.

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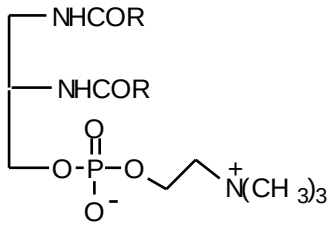
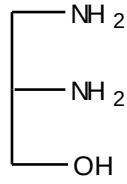
catalysis to give the dihydrochloride. Although this synthesis affords a reasonable overall yield (42%, based on **16**) it has the severe disadvantage of proceeding through the potentially explosive¶ diazide **17** and also of affording only racemic material. The synthesis has, however, been adapted to give both the (*R*) and (*S*)-2,3-diaminopropan-1-ol by a resolution step using D(+)- or L(-)-tartaric acid, respectively,[4] but it is not attractive for preparation of large amounts of diamino alcohol **2**.

In initial studies in our laboratory[5] we have used the route in **Scheme 2**, to prepare small amounts of the tetrahydropyran protected diamine which was then *N*-acylated before hydrolysis to give a diamido alcohol which was then further reacted to give diamide analogues of phosphatidylcholine **1**. Our wish to prepare other related derivatives, especially in chiral form, led us to investigate alternative procedures for the preparation of the key intermediate **2**.



1



2

¶ It should be noted that although sodium azide is routinely used for preparation of alkyl azides, sodium azide is potentially hazardous[2] and the use of sodium azide in dichloromethane can also lead to explosions due to the possible formation of diazidomethane. Tetramethylguanidium azide in non-halogenated solvents has been recommended as a safe alternative.[3]

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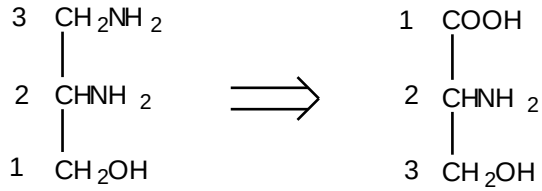
2.3. Syntheses Based on D-, L- and DL-Serine¶

A simple retrosynthetic analysis of diamino alcohol **2** (**Scheme 3**) leads to serine as the most obvious starting material, especially in view of the fact that both chiral forms of the amino acids are available (see page 13). Clearly, the synthetic strategy requires that the 2-amino and 3-hydroxy groups of serine are protected, singly or together, and that the carboxyl group is converted to an aminomethyl function. The presence of an alcohol and amine functionality within a molecule can cause problems in selective reactions since both possess acidic hydrogen and both possess lone pairs of electrons. However, significant reactivity differences do occur because of electronegativity differences. Thus, alcohols are more acidic than amines and amines are more basic than alcohols.



2 Serine

Scheme 3 Retrosynthesis of 2,3-diaminopropan-1-ol

¶ It should be noted that an amino acid based synthesis of the DL-2,3-diaminopropan-1-ol dihydrochloride (**2** .2 HCl) has been briefly reported[6] without experimental detail, by $LiAlH_4$ reduction of a di-Boc derivative of 2,3-diaminopropionic acid methyl ester followed by a hydrolysis of the protected diamine. We have not used this for our work since the starting material 2,3-diaminopropanoic acid hydrochloride is relatively expensive (1 g, £ 9)[7] and use of this material would again not afford a chiral product.

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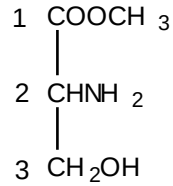
The greater availability of the lone pair on nitrogen towards electrophilic attack compared to oxygen allows the important selective acylation of amine groups in the presence of hydroxy groups[8] and therefore it is possible to acylate selectively (*e.g.*, with $PhCH_2OCOCl$) serine on nitrogen to form the *N*-Cbz derivative.[9,10] Other common *N*-protection groups are, for example, *t*-butyloxycarbonyl (Boc), 2-(4-biphenylyl)-isopropoxycarbonyl (Bpoc), 9-fluorenyl-methoxycarbonyl (Fmoc) and triphenylmethyl (trityl, Tr). More detailed information on specific protecting groups for amino acids is available in the literature.[11-15] Further consideration of serine chemistry and of possible starting materials suggested that the serine methyl ester **18** (as its hydrochloride) would be a more convenient starting point than serine itself and in all of our studies, we have used the ester **18** either in racemic DL- or chiral L-form.



18

A consideration of the literature suggested essentially two useful approaches towards modification of serine or its esters, both involving protection of the 2-NH_2 and 3-OH groups through a common protecting group, introduced either into **18**, its *N*-benzyl-oxycarbonyl derivative **19**, or its *N*-*t*-butyloxycarbonyl (*N*-Boc) derivative **20**. These approaches are shown in **Scheme 4a** and **4b**, which afford the 4,5-dihydrooxazole **21** and the oxazolidines **22** and **23**, respectively.

The main reaction in **Scheme 4a**, which uses ethyl benzimidate, was first described in 1949 by Elliot[16] but was later exploited by Meyers and co-workers[17] in a synthesis of a chiral auxiliary (*S*)-2-amino-3-methoxy-propan-1-ol.

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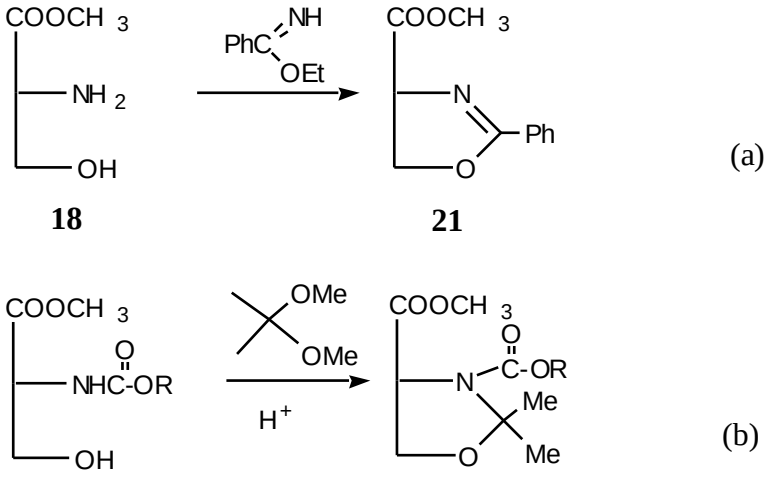

18 **21**

19 R= CH_2Ph
20 R= $C(CH_3)_3$

22 R= CH_2Ph
23 R= $C(CH_3)_3$

Scheme 4

Both the *N*-benzyloxycarbonyl and the *N*-*t*-butyloxycarbonyl derivatives of methyl serine ester, compounds **19** and **20,** respectively, have been reacted with acetone or its equivalent, 2,2-dimethoxypropane, to afford the *N*, *O*-protected derivatives, oxazolidines **22** and **23**, respectively. Thus, in a recent study towards manzamines, Pandit and co-workers[10] reacted L-**19** (**19c** in our terminology) with 2,2-dimethoxypropane under acid catalysis to afford **22** (=**22c**) in high yield following a similar reaction which Garner and Park[18] had used to prepare **23** in 95% yield from the corresponding *N*-Boc derivative of serine **20**.¶

A very recent report[19] describes a one-pot reaction of L-serine with formaldehyde followed by benzyloxycarbonyl chloride to give in high yield the oxazolidine **24** (**Scheme 5**). Although we have not used this reaction in our work it seems to offer good potential for future development for the synthesis of **2**.

¶ Compound **23** is the important intermediate in the preparation of the so-called "Garner aldehyde", which is important in chiral synthesis.

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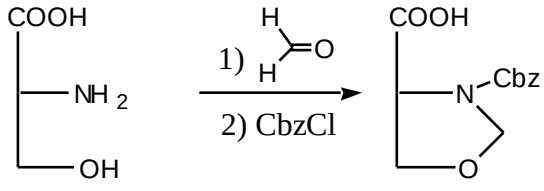
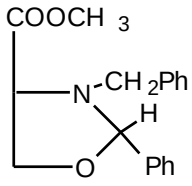


L-Serine **24**

Scheme 5

In our own work, the 4,5-dihydrooxazole and oxazolidine approach to protect the amine and hydroxyl group has been used successfully and these are described in more detail in subsections **2.3.1** and **2.3.2**, respectively. In the later section (see page 37), a novel reaction which led, surprisingly, to an *N*-benzyl protected 2-phenyloxazolidine **25** in a one-step process is also described.



25

2.3.1. Synthesis *via* 4,5-Dihydrooxazole Derivatives

Both Elliot[16] and Meyers and co-workers[17] described the use of ethyl benzimidate to prepare the 4,5-dihydrooxazole **21** although neither described how to prepare the benzimidate itself, which is only available commercially as its hydrochloride. Therefore we prepared the free imidate by extraction into dichloromethane from a basified solution in water. Evaporation of the combined extracts gave crude material which was used immediately. Reaction of the benzimidate with DL-serine methyl ester hydrochloride **18** ·HCl in 1,2-dichloroethane, essentially as described by Meyers,[17] led to precipitation of material assumed

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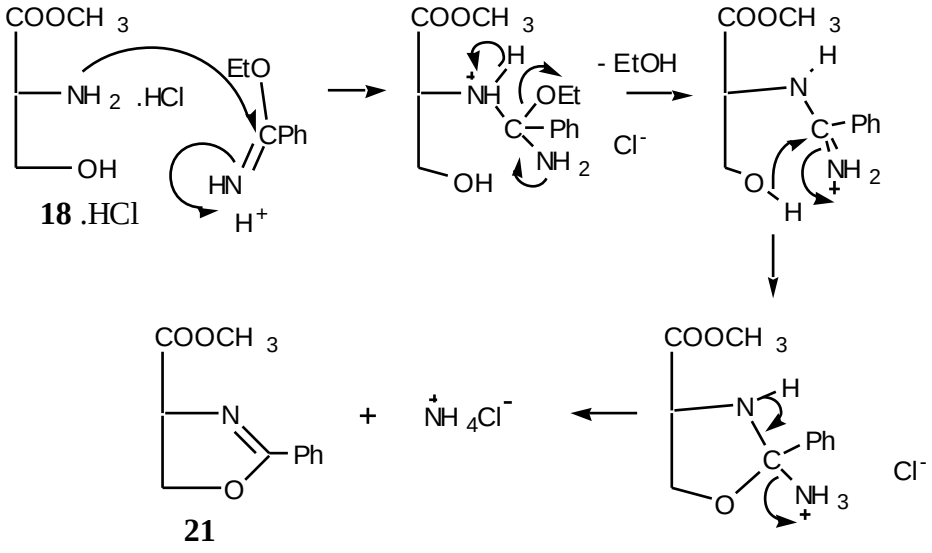
to be ammonium chloride (**Scheme 6**) and work up of the filtered reaction solution gave the expected racemic methyl (4*RS*)-4,5-dihydro-2-phenyloxazole-4-carboxylate **21**, which was not purified but was used immediately.



Scheme 6

Curiously, Meyers and co-workers[17] did not report the removal of any salt and yet claimed to have isolated analytically pure material by simply evaporating the reaction solution. This cannot be the case since ammonium chloride is a by product of the reaction (**Scheme 6**) and the description of their experimental procedure cannot be completely accurate.

Conversion of the ester **21** to the corresponding racemic amide by treatment with ammonia in methanol was readily achieved (**Scheme 7**), and the amide **26** crystallised directly from the reaction solution. Careful isolation of further crops of material after charcoal treatment afforded, after recrystallisation of combined material, a total yield of 75% of the racemic amide as a high melting crystalline solid. The ^{1}H NMR spectrum of this material and particularly the IR spectrum, which showed typical amide absorptions, fully supported the expected structure.

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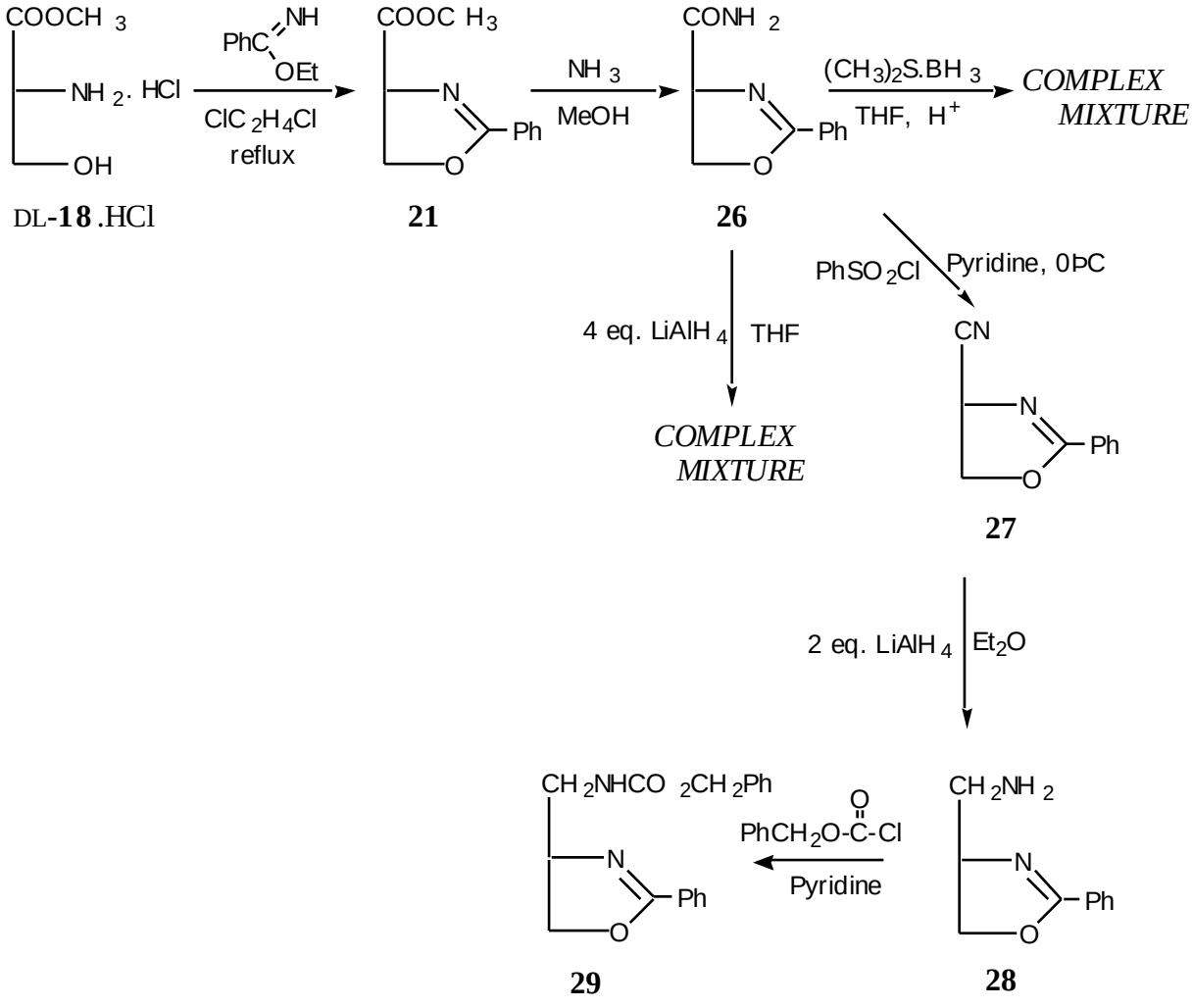

Scheme 7

The original synthetic plan was to reduce the amide **26** directly to the corresponding amine **28** using typical amide reducing agents such as lithium aluminium hydride or borane-dimethyl sulfide complex. Such a reduction provides a quick route to the required racemic diamino alcohol **2** from serine methyl ester hydrochloride **18** ·HCl (four steps overall), since diamine **2** should be readily formed (in salt form) from the amine **28** by simple acid hydrolysis. There is previous work and experience from our laboratory which suggests that such a reduction would be successful.[20]

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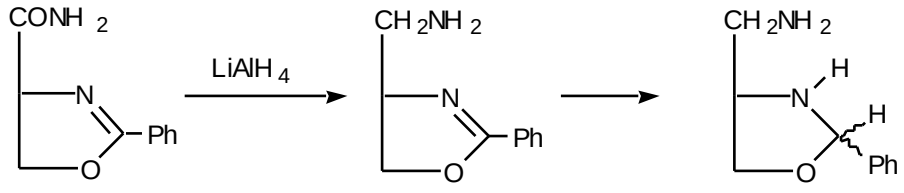
As it turned out, the reduction of the amide **26** provided considerable difficulty. One possible source of difficulty is the fact that over reduction can lead to oxazolidine derivatives as shown in **Scheme 8** by reduction of the carbon to nitrogen double bond in



26 **28** oxazolidine derivatives

Scheme 8

dihydrooxazole ring of **28**. Although this would not spoil the overall synthesis, since acidic hydrolysis of the oxazolidine ring would also afford the required diamino alcohol **2** salt, the reduction might lead to mixtures. It should be noted that two isomers of the oxazolidine (the *cis* and *trans* forms) are possible. However, although the possibility of over reduction has been noted in the case of the corresponding ester **21**,[21] it was claimed that, with careful choice of the ratio of the substrate to reducing agent, reduction of the ring could be avoided. We chose in our work to use an excess of lithium aluminium hydride to drive the reaction to give the oxazolidine. Reaction of the amide **26** with 4 molar equivalents of the metal hydride gave accordingly to TLC a multi component mixture and the ^{1}H NMR spectrum of the product was more complicated than expected. Attempted separation by column chromatography appeared unattractive due to the complex nature of the mixture. Therefore, we decided to examine an alternative reducing agent, borane-dimethyl sulphide comlpex which has been used previously for amide to amine reductions.[22,23] However, this reaction also gave a complex mixture (see later) and because of possible difficulties separating and identifying components of this mixture of reaction products, we decided to attempt the lithium aluminium hydride reduction of the corresponding racemic nitrile **27** which may

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readily be obtained from the amide **26**. Thus treatment of the amide **26** with benzenesulfonyl chloride in pyridine (**Scheme 7**) afforded as crystalline solid the racemic nitrile **27,** in high yield. The spectral properties of the product were as expected although it was noticeable that the nitrile absorption at 2250 cm^{-1} was extremely weak. At the start of our work the nitrile had not been described, but in a recent publication, Cossu and co-workers[24] reported its preparation, without experimental details, by a similar reaction using *p*-toluenesulfonyl chloride on the racemic **26**. The m.p. of our racemic material was 57.7-58.3˚C which is higher than that reported[24] by Cossu and co-workers who gave the m.p. 49-51˚C for the same compound. However, the data reported for the ^1H NMR spectrum and IR spectrum were similar to that which we obtained.

Reduction of the nitrile **27** was attempted using excess of lithium aluminium hydride in diethyl ether. Work up afforded an oil which, assuming it was the required amine **28**, was obtained in 71% yield after extraction of the inorganic products. Although this material was not purified it showed the expected absorptions for NH (3500-3000 cm^{-1}) and C=N (1650 cm^{-1}). We decided to attempt to purify this compound as its *N*-benzyloxycarbonyl derivative **29** and reaction of the amine **28** with the benzyloxycarbonyl chloride (**Scheme 7**) in the usual manner gave, after purification by column chromatography, an oil in low yield, having an elemental analysis close to that expected. The spectral properties were also in agreement with the product being the required *N*-benzyloxycarbonyl derivative but, because of the poor yield, this possible route to diamino alcohol **2** was not investigated further.

As mentioned previously, attempted reduction of the racemic amide **26** using borane dimethyl sulphide complex in tetrahydrofuran gave a complex mixture of products according to TLC, and because we decided to investigate an alternative route to the diamino alcohol **2** (see Section **2.3.2**.) this route was abandoned, but it may repay further investigation in the future.

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2.3.2. Syntheses *via* Oxazolidine Derivatives

The work carried out in this section was performed both in the racemic series, starting with DL-serine methyl ester hydrochloride **18** ·HCl and also in the chiral series starting with L-serine methyl ester hydrochloride L-**18** ·HCl.¶

The discussion of our experimental work is largely confined to the racemic series except where special notes are required on the chiral properties. Initially the reaction sequence (**Scheme 9**) is based on the work of Pandit and co-workers[10], in the L- series, for the conversion of the *N*-benzyloxycarbonyl serine methyl ester hydrochloride **19c** ·HCl (originally described by Hassal and Thomas[9]) *via* the dimethyl oxazolidine **22c** and the alcohol **30c** to the tosylate **31c**. Thus treatment of the DL-serine methyl ester **18** ·HCl with benzyloxycarbonyl chloride in aqueous sodium hydrogen carbonate gave the low melting derivative **19** in high yield which, after a rather difficult recrystallisation, afforded analytically pure material. The structure of this compound was fully supported by its ^{13}C NMR spectrum which had not been previously reported.

Treatment of **19** with 2,2-dimethoxypropane under acid catalysis afforded crude material which on column chromatography gave the analytically pure oxazolidine **22** in 84% yield. The IR spectra confirmed the disappearance of the NH and OH groups and the ^{1}H spectra showed the expected signals for the geminal dimethyl group at δ 1.50, 1.57, 1.64 and 1.71. The fact that four signals rather than two are observed points to the occurrence of restricted rotation about the amide bond in this compound, and this was

¶ The racemic and chiral series of compounds, except for the starting material serine methyl ester hydrochloride **18** ·HCl, are distinguished by using the desriptor "c" for the chiral compounds. Thus, **19** and **19c** represent, respectively, *N*-benzyloxycarbonyl-serine methyl ester derivatives from DL-serine or L-serine. The starting materials, DL- and L-serine methyl ester hydrochloride are distinguished by the descriptors **18** ·HCl and L-**18** ·HCl to retain the relationship to the naming of the amino acids.

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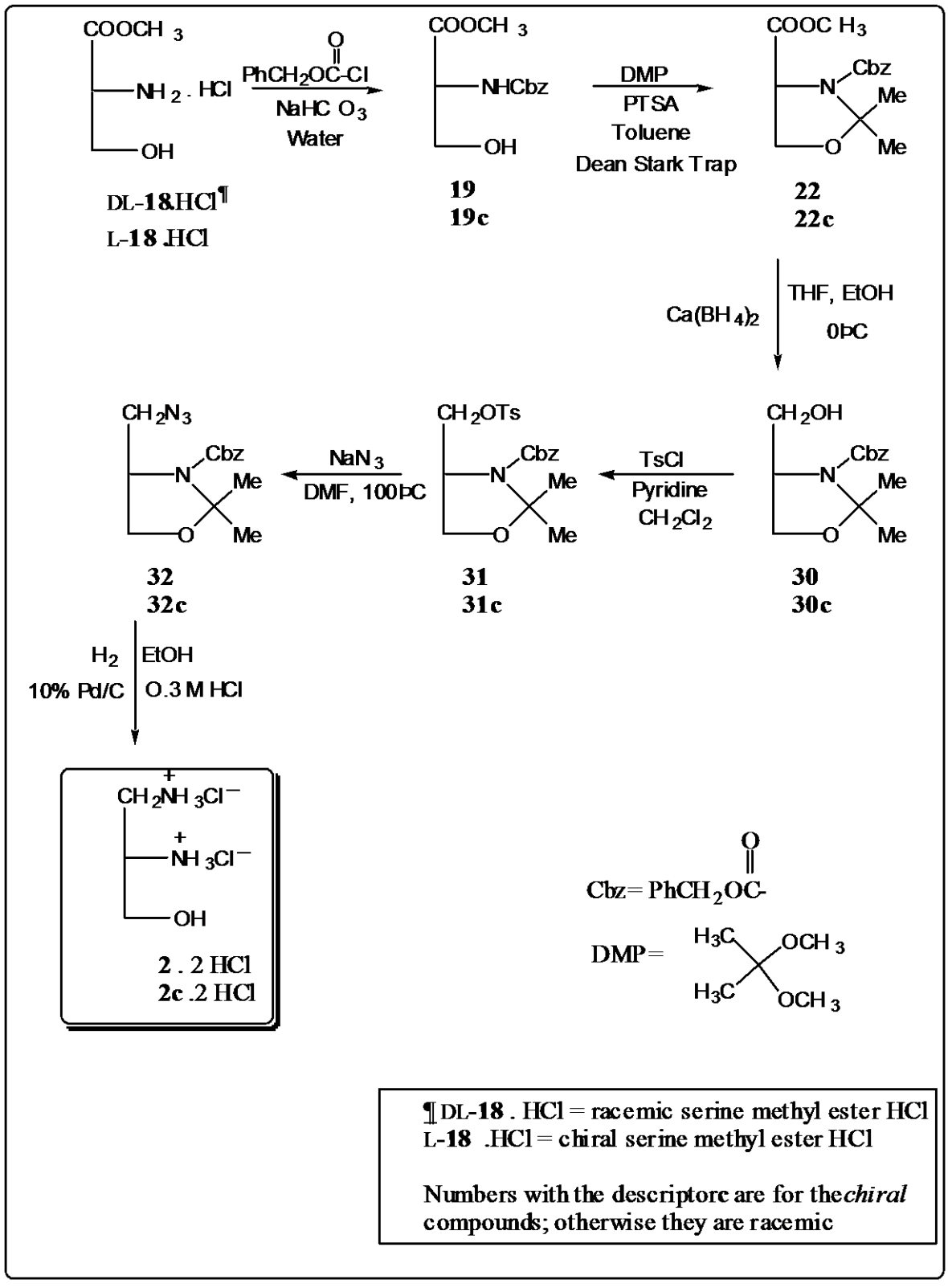

Scheme 9

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further supported by observing four signals also for the methyl carbons in the ^{13}C NMR spectrum. Pandit and co-workers[10] also have observed this phenomena in the ^{1}H NMR spectra of the corresponding chiral compounds. A similar phenomena is observed in the ^{1}H NMR spectrum of *N,N*-dimethylformamide.

Reduction of the ester group via oxazolidine **22** by the reported[10] procedure using the mixed sodium borohydride-calcium chloride reagent [probably $Ca(BH_4)_2$] afforded the expected alcohol **30** (**Scheme 9**). After column chromatographic purification the analytically pure alcohol **30** was obtained as an oil in 95% yield. The IR spectra showed the presence of OH at 3456 cm^{-1} and disappearance of the C=O absorption found at 1756 cm^{-1} in **22**. The existence of rotamers was again suggested by peak broadenings in the NMR spectra of this compound.

Reaction of alcohol **30** with *p*-toluenesulfonyl chloride in pyridine as in the procedure reported[10] in the L- series gave after column chromatography the tosylate **31**, as an oil in 93% yield. It should be noted that in the chiral series, as reported by Pandit and co-workers[10] and also observed in our own work, the corresponding tosylate is crystalline. The spectral details of this compound are in accordance with its expected structure and hindered rotation of the amide bond was again apparent from peak broadening.

Displacement of the *p*-toluenesulfonyloxy group in **31** with azide ion was carried out by treatment with sodium azide in *N,N*-dimethylformamide at 100˚C for 6 h. Isolation with column chromatography gave the analytically pure azide **32** as an oil in 84% yield, having a characteristic absorption at 2107 cm^{-1} from its IR spectra (see Appendix, spectrum 3). Measurement of its ^{1}H NMR spectrum at 270 MHz and its ^{13}C NMR spectrum at 67.9 MHz (Appendix, spectra 1 and 2, respectively) showed again four signals for the methyl protons and the methyl carbons, respectively, indicating restricted rotation about its amide bond.

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Conversion of the azide **32** into the final target molecule, the diamino alcohol **2** requires;

(**i**) Reduction of the azido group to the amino group,

(**ii**) Removal of the benzyloxycarbonyl protecting group,

(**iii**) Hydrolysis of the isopropylidene protecting group.

This was achieved in one step by catalytic hydrogenation and hydrogenolysis of azide **32** in ethanol¶ containing hydrochloric acid. Thus the hydrogenation N_3 'NH_2 and hydrogenolysis of the benzyloxycarbonyl group was brought about by the H_2/Pd-C treatment, and acid hydrolysis of the isopropylidene group followed by salt formation was achieved by the hydrochloric acid present in the ethanol.

The crude dihydrochloride was obtained on evaporation of the solvent after removal of the catalyst, but further extraction of the Pd-C catalyst was necessary to obtain a good recovery of the product. Recystallisation from methanol was made difficult by the fact that solution occurred only slowly, even in hot methanol but nice crystals of analytically pure material were obtained on prolonged storage of the solution at room temperature. Further crops were obtained from further storage at 4°C. The m.p. of the diamino alcohol salt **2** ·2 HCl (176-178°C) was close to the reported value of 172-174°C by Okomato and Barefield.[1] The^{13}C NMR spectrum was very characteristic for the compound in showing just three signals at δ 40.6, 52.21 and 61.01 for CH_2NH_3, $CHNH_3$ and CH_2OH, respectively.

An attempt to separate the enantiomers present in the racemic mixture on a chiral TLC plate [Chiral plate® MacheryNagel MN/811 056 - a TLC plate coated with a

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¶ Later study showed that the use of methanol instead of ethanol simplified the isolation of the product **2**·2 HCl from the reaction mixture. The compound **2** ·2 HCl is absorbed on the catalyst and is more easily extracted by methanol.

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reversed phase silica gel and impregnated with a chiral proline-derived selector and Cu (II) ions] was unsuccessful. An attempt to resolve the ^{1}H NMR spectra of the racemic mixture by use of a chiral shift reagent {Tris[3(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III)] was complicated by the fact that the compound **2** ·2 HCl itself was insoluble in most of the useful NMR solvents and clearly water could not be used. An attempt to use dimethyl sulfoxide as the NMR solvent with the shift reagent did not gave a successful result. Use of a chiral shift reagent may be possible if a suitable derivative of **2** ·2 HCl, soluble in organic solvents (for example the triacetyl derivative) is used in the NMR experiment.

The complete set of reactions in **Scheme 9** were than repeated using the chiral L-serine methyl ester hydrochloride (L-**18** ·HCl) as the starting material, through intermediates **19c**, **22c**, **30c**, **31c**, **32c** to give finally the target chiral (*S*)-2,3-diaminopropan-1-ol dihydrochloride **2c**·2 HCl. All spectral properties of the compounds in the chiral series were directly analogous to those in the racemic series and all of the compounds gave satisfactory elemental analyses. Curiously our value of the m.p. for **31c** of 72-74°C differs from that reported[10] (82-86°C) although it is interesting that our rotation {$[\alpha]_D$ -43.6°} is slightly lower than that reported {$[\alpha]_D$ -39°}. The rotation of the azide **32c**, a compound previously not reported, was $[\alpha]_D$ -33.9° (CH_2Cl_2) which agrees well, except for the obvious change in sign with the value of +32.8° found for the enantiomer.[25] The rotations of compound **2c** ·2 HCl were recorded in both methanol and water solutions at various wavelengths and a graph showing these is given in the Appendix. Current work in our laboratory has now given the enantiomer of **2c** ·2 HCl, which shows a distinct difference in rotation to that expected. For example, in water for **2c** ·2 HCl, $[\alpha]_D$ has a value of -13.3° whereas for the material prepared in the enantiomeric series $[\alpha]_D$ is +7.64°, close to that reported[4] $[\alpha]_D$ +7.1° for material obtained by resolution of the racemic material with tartaric acid. Clearly, it is of great importance to measure the enantiomeric purity of the two materials prepared in our own work. Use of chiral chromatographic HPLC may provide an answer.

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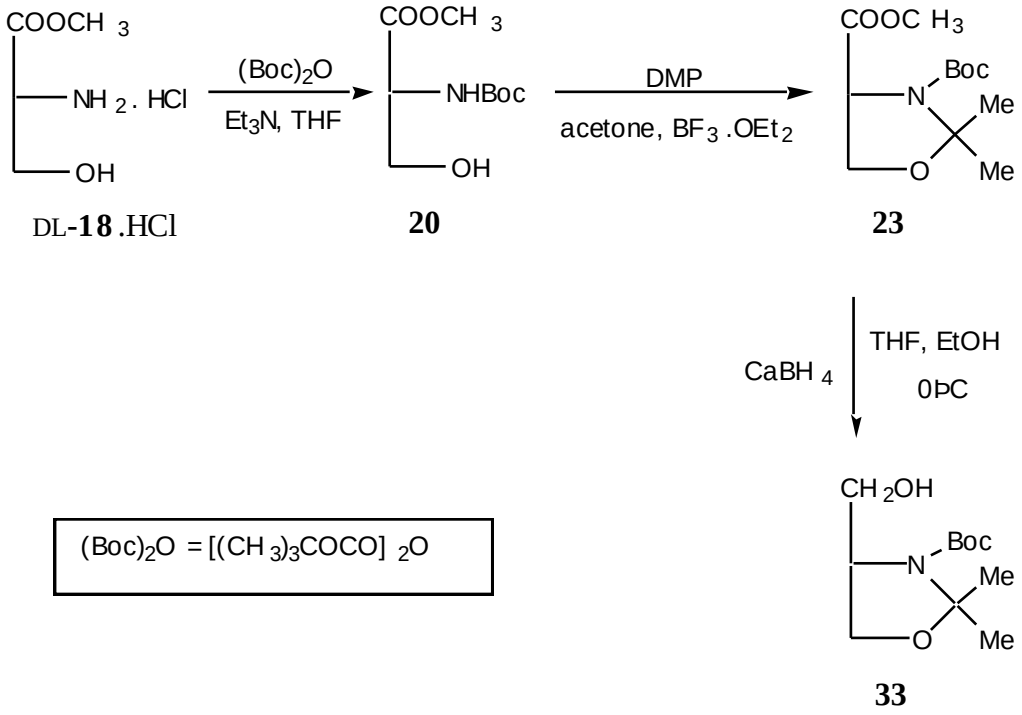
Alongside our work with the successful synthesis in **Scheme 9**, we investigated a similar series of reactions using the *t*-butyloxycarbonyl (Boc) protecting group instead of the benzyloxycarbonyl (Cbz) group. This series of reactions, carried out only with racemic material (**18** ·HCl), is shown in **Scheme 10**. The first two steps (**18** ·HCl '➞ **20**' ➞ **23**) followed the literature method for the chiral series[26] and borohydride reduction of **23** gave the crystalline alcohol **33** in analytically pure form. Due to the success in our other route (**Scheme 9**) work on this series was not continued further.



DL-**18** .HCl **20** **23** **33**

Scheme 10

In an investigation of a proposed alternative route using the known[27] *N*-benzyl-DL-serine ester **34** which we intended to convert to the derivative **35,** the reductive alkylation of DL-serine methyl ester **18** ·HCl was carried out with benzaldehyde (**Scheme 11**) in the reported manner.[27] Careful examination by TLC showed four components present in the reaction product of which only two appeared to be derived from serine. Separation by column chromatography gave in only 21% yield the expected *N*-benzyl derivative **34** with ^{1}H NMR spectroscopic properties (see Appendix, spectrum 8a) in agreement with those reported.[27]

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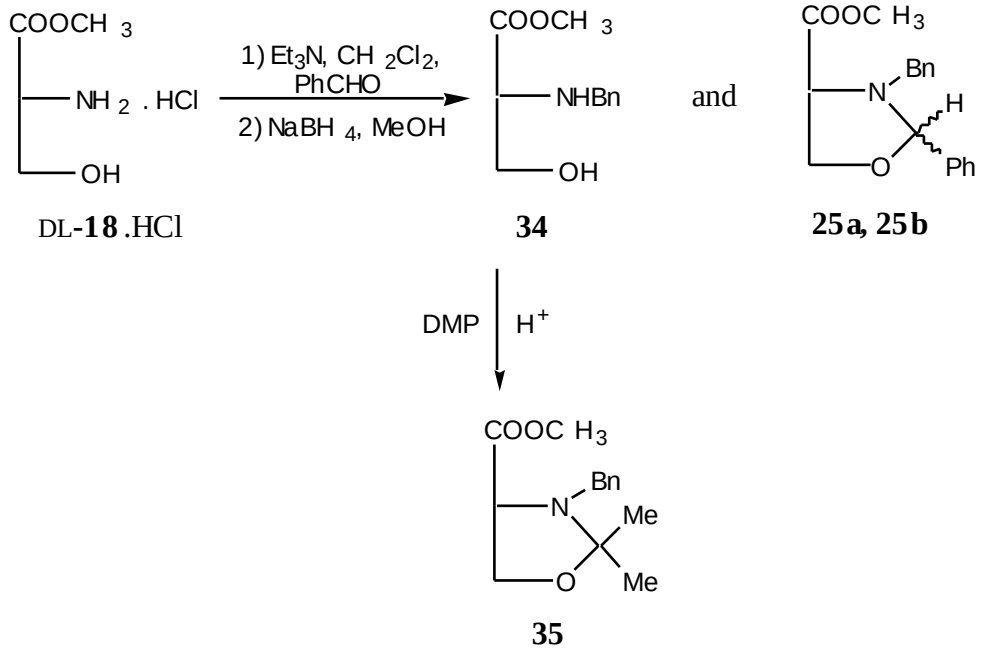
The elemental analysis of the other product derived from serine, analysed for $C_{18}H_{19}NO_3$, suggesting two molecules of benzaldehyde had reacted with **18**. The ^1H NMR spectrum (see Appendix, spectrum 8b) supported this suggestion and importantly showed two signals at δ 5.20 and 5.60, integrating together for one proton, which could be assigned to a benzylidene proton (Ph-C*H*). The IR spectrum showed no absorption for OH, and from both pieces of evidence we deduced the structure as the *O,N*-benzylidene derivative of *N*-benzyl serine methyl ester compounds **25a** and **25b**, which exist in *cis* and *trans* forms due to stereoisomerism at C-2 of the oxazolidine ring. Although we have not yet obtained **25a** and **25b** in high yield, this double protected serine intermediate would also be useful for conversion into the diamino alcohol **2**. Since this compound can be made in a single one-step process from the starting material serine methyl ester **18**, its use is attractive in this type of synthesis.



DL-**18**.HCl **34** **25a, 25b**

35

Scheme 11

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2.4. Conclusions

The research in this project has shown that it is possible to prepare in racemic and also in chiral form 2,3-diaminopropan-1-ol, which is required for further transformations into the chiral phosphatidylcholine derivatives needed for anti-HIV testing.

Unfortunately, time did not allow for carrying out for the final steps, reaction at the hydroxyl group with 2-chloro-1,3,2-dioxaphospholan-2-one (ethylene chlorophosphate) followed by the opening of the heterocyclic ring with trimethylamine.[5] However, this work has established the basis for developing the project in the future and will by suitable modification allow the preparation of chiral 1,2,3-triaminopropane derivatives which can also be converted into interesting phosphatidylcholine analogues.

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CHAPTER 3

EXPERIMENTAL

3. EXPERIMENTAL

3.1. General methods

Analytical TLC was performed on precoated glass backed TLC plates, 0.25 mm silica gel with fluorescent indicator UV_{254}, obtained from Camlab®. Compounds were detected with either a 254 nm UV lamp, or by spraying the plate with an aqueous solution containing cerric sulfate (1%, w/v), molybdic acid (1.5%, w/v) and sulfuric acid (10%, v/v) or a solution of ninhydrin (0.1%, w/v) in acetone spray followed by heating to 150°C. Column chromatography was performed on Matrex® Silica 60 (70-200 μm mesh, Fisons) or Kieselgel 60 (70-230 μm mesh, Merck). Melting points were taken on hot stage apparatus, and are uncorrected. Optical rotations were measured on a Perkin-Elmer model 141 polarimeter. Elemental analyses were performed by Mr. A. Saunders at the University of East Anglia. IR spectra were recorded on Perkin-Elmer model 298, 297 or Perkin-Elmer FT-IR model 1720x spectrophotometers. ^{1}H NMR spectra were recorded on Jeol PMX60SI, EX90 FT or EX270 FT NMR spectrometers in $CDCl_3$ unless stated otherwise, with tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded using a JEOL EX90 FT spectrometer at 22.6 MHz or a JEOL EX270 FT spectrometer at 67.9 MHz in $CDCl_3$ unless stated, with tetramethylsilane as an internal standard. *J* values are given in Hz.

Reagents were obtained from Aldrich, Sigma or Lancaster. Tosyl chloride (TsCl) was recrystallised from toluene containing 5%, v/v acetyl chloride. When required, dry solvents were obtained as follows: DMF, MeOH, EtOH and toluene were dried over activated 4Å molecular sieves. THF was dried by distillation from calcium hydride. As an alternative to laboratory drying, HPLC grade solvents were used. Light petroleum was of boiling range 40-60°C unless stated otherwise. Organic solutions were dried over anhydrous sodium sulfate or magnesium sulfate. Solvent ratios are given as v/v.

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Note on designation of chirality: Traditionally, the chiral amino acids have been described as D- or L- isomers, but this nomenclature cannot be used when acyclic amino acids are converted to cyclic derivatives, for which the *R*, *S*- nomenclature is necessary. L-Serine corresponds to (*S*)-serine, and we have followed precedent and retained the D- and L- descriptors for our starting amino acid and its acyclic derivatives.

3.2. Experimental Procedures

*Methyl (4*RS*)-4,5-Dihydro-2-phenyloxazole-4-carboxylate* **21**.— This preparation was carried out essentially as previously described.[1] To a solution of ethyl benzimidate¶ (13.4 g, 89.8 mmol) in 1,2-dichloroethane (200 mL) was added DL-serine methyl ester hydrochloride DL-**18** ·HCl (15.5 g, 99.6 mmol) and the mixture was then heated under reflux for 24 h. The reaction mixture was filtered from the salts formed and the filtrate was concentrated and dried to yield, as a syrup (R_f 0.65 in ethyl acetate), compound **21** (17.13 g, 93%).

¶ The organic solution of ethyl benzimidate was prepared as follows: Ethyl benzimidate hydrochloride (18.2 g, 99.1 mmol) was dissolved in saturated aqueous potassium carbonate (200 mL) and the solution was extracted with dichloromethane (2 x 50 mL). The combined organic extracts were washed with water (3 x 40 mL) dried (Na_2SO_4) and then concentrated to afford, as an oil, ethyl benzimidate (13.4 g) which was immediately taken up into 1,2-dichloroethane (200 mL) for use in the reaction.

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*(4*RS*)-4,5-Dihydro-2-phenyloxazole-4-carboxamide* **26**.— Ammonia gas was passed through a solution of **21** (16.83 g, 82 mmol) in methanol (120 mL) at 0° C for 1 h during which time a precipitate of the required product was formed. The resultant suspension was stored overnight at 20°C during which time further crystallisation of the product occurred. The solid was collected by filtration and washed with methanol (3 x 20 mL) to give crystalline material (10.39 g, 67%, m.p. 169.6-169.9°C). The filtrate was treated with

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charcoal under reflux for 30 min, filtered and concentrated to yield a further crop of crystalline material (1.26 g, 8%, m.p. 168.1-169°C). Recrystallisation of a small sample (0.5 g) of the second crop from methanol gave the analytical compound (R_f 0.3, in ethyl acetate) of **26**, m.p. 169.6-169.7˚C (Found: C, 63.2; H, 5.2; N, 14.7. $C_{10}H_{10}N_2O_2$ requires C, 63.15 H, 5.3; N, 14.7%); $\nu_{max.}$(Nujol)/cm^{-1} 3380 and 3200 (br, NH), 1650 (CO and C=N); δ_H (60 MHz; $CDCl_3$) 4.40-5.00 (3 H, m, 4-H, 5-H_2), 5.80-6.40 (1 H, br s, NH), 6.42-7.00 (1 H, br s, NH), 7.20-7.62 (3 H, m, 3'-H, 4'-H, 5'-H), 7.80-8.20 (2 H, m, 2'-H, 6'-H)¶

*(4*RS*)-4,5-Dihydro-2-phenyloxazole-4-carbonitrile* **27**.— To a stirred solution of amide **26** (5.3 g, 27.9 mmol) in pyridine (75 mL) at 0˚C was added dropwise benzenesulfonyl chloride (15.3 mL, 21.18 g, 119 mmol). Stirring was continued at 0°C for 2 h, and the solution was then stored for 3 days at 20°C. The reaction mixture was poured onto crushed ice (75 g) and saturated aqueous sodium hydrogen carbonate solution (15 mL) was added. The resultant mixture was extracted with dichloromethane (3 x 50 mL) and the combined extracts were then washed with water until the extracts were neutral (pH= 7), dried and concentrated to yield crude crystalline nitrile **27** (4.5 g). Column chromatography [ethyl acetate:petroleum ether (1:3)] afforded, as a crystalline material (R_f 0.75 in the same system), compound **27** (4.03 g, 84%), m.p. 57.7-58.3˚C (lit.,[2] 49-51°C) (Found: C, 69.8; H, 4.5; N, 16.1. $C_{10}H_8N_2O$ requires C, 69.8; H, 4.7; N, 16.3%); $\nu_{max.}$(Nujol)/cm^{-1} 2250 (w, C-N), 1640 (C=N), no absorption in range 3500-3100; δ_H (60 MHz; $CDCl_3$) 4.46-4.76 (2 H, m, 5-H_2), 5.04 (1 H, dd, $J_{4,5}$ 7.2 and $J_{4,5'}$ 9.6, 4-H), 7.20-7.70 (3 H, m, 3'-H, 4'-H, 5'-H), 7.76-8.20 (2 H, m, 2'-H, 6'-H).

¶ Prime numbers refer to the aromatic moiety in this spectrum and related spectra.

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*(4*RS*)-4-Aminomethyl-4,5-dihydro-2-phenyloxazole* **28**.— To a solution of **27** (0.95 g, 5.5 mmol) in diethyl ether (30 mL) was added lithium aluminium hydride (0.42 g, 11.1 mmol) in one portion and the mixture was stirred at 0°C for 2 h and then stored at 20°C for 1h. To the stirred solution was added water (0.12 mL) and after 5 min, aqueous sodium hydroxide solution (3 M, 0.12 mL), followed after a further 5 min by water (0.36 mL). Stirring was continued for further 5 min and the resultant precipitate was removed by filtration. The filtrate on concentration yielded a crude oil **28** (0.32 g, 33%). Extraction of the collected solids in dichloromethane with Soxhlet apparatus for 1 h, and evaporation of the solvent gave as an oil a further amount of crude compound **28** (0.37 g, 38%). The IR spectra of both materials were identical; $\nu_{max.}$(neat)/cm^{-1} 3500-3000 (br, NH), 1650 (C=N). The compound **28** was not purified further.

(*4*RS*) -4 (*N-*Benzyloxycarbonylaminomethyl)-4,5-dihydro-2-phenyloxazole* **29**.— To a solution of crude **28** (0.3 g, 1.7 mmol) in pyridine (5 mL) was added benzyloxycarbonyl chloride (0.61 mL, 4.3 mmol) and the mixture was stirred for 12 h. Water (0.5 mL) was then added and the reaction mixture was stirred for 1 h, after which time it was then poured onto saturated aqueous sodium hydrogen carbonate solution (50 mL). The organic phase was separated, extracted with dichloromethane (2 x 25 mL) and the combined organic phases were dried and concentrated to yield an oil (0.36 g) containing a major component [R_f 0.4 in ethyl acetate:hexane (5:2)] which was isolated by column chromatography in the same system to give as an oil the title compound **29** (0.08 g, 15%), (Found: C, 69.0; H, 5.7; N, 8.9. $C_{18}H_{18}N_2O_3$ requires C, 69.7; H, 5.85; N, 9.0%); $\nu_{max.}$(neat)/cm^{-1} 3600-3100 (br, NH), 1710 (br, CO), 1640 (C=N); δ_H (60 MHz; $CDCl_3$) 3.20-3.80 (2 H, complex, C*H*$_2$NHCO), 3.96-4.60 (3 H, complex, 4-H, 5-H$_2$), 5.12 (2 H, s, C*H*$_2$Ph), 5.28-5.72 (1 H, br t, NH), 7.08-7.60 (3 H, m, 3'-H, 4'-H, 5'-H), 7.72-8.12 (2 H, m, 2'-H, 6'-H).

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Reduction of Amide **26**.— *(a) With lithium aluminium hydride.*— To a solution of amide **26** (0.5 g, 2.63 mmol) in THF (10 mL) was added lithium aluminium hydride (0.61 mL, 4.3 mmol) and the mixture was stirred for 12 h. Water (0.1 mL) was added to the stirred solution, followed by aqueous sodium hydroxide solution (3 M, 0.12 mL). The resultant mixture was stirred for 5 min, then a further amount of water (0.36 mL) was added and stirring was continued for further 5 min. The precipitate was removed by filtration and the filtrate was concentrated to yield an oil. TLC examination showed a complex mixture of several products including the starting material and the mixture was not investigated further.

(b) With borane-dimethyl sulfide.— The procedure is based on that described by Brown and co-workers.[3] To the amide **26** (0.5 g, 2.6 mmol) was added borane-dimethyl sulfide complex in THF (2.0 M, 2 mL, 3.0 mmol) under nitrogen atmosphere and the resultant solution was heated under reflux for 4 h. THF (1 mL) was added to the reaction mixture followed by hydrochloric acid (6 M, 0.43 mL). The resultant precipitate was removed by filtration and the filtrate was neutralised with NaOH pellets. This mixture was stored overnight at room temperature, and after filtration, was concentrated to yield an oil (0.64 g) which was shown to be a complex mixture of products by TLC. This mixture was not investigated further.

N-*Benzyl*-DL-*Serine Methyl Ester* **34** *and* cis- *and* trans- *Isomers of Methyl (4*RS*)-3-benzyl-2-phenyloxazolidine-4 carboxylate* **25a** *and* **25b**.— The procedure followed was that as described by Barco and co-workers.[4] Thus, to a stirred solution of DL-serine methyl ester hydrochloride DL-**18** ·HCl (7.87 g, 50.6 mmol) in dichloromethane (50 mL) were added (dropwise) sequentially triethylamine (7.3 mL, 52.5 mmol) and benzaldehyde (5.2 mL, 51.2 mmol). Anhydrous magnesium sulphate (5 g) was then added and the mixture stirred for 24 h at room temperature. The mixture was then filtered and the filtrate was concentrated to give a residue which was dissolved in methanol (100 mL). To the resulting solution was added

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sodium borohydride (1.9 g, 50.2 mmol) portion wise at 0°C (gas evolution) and the reaction mixture was stirred for a further 4 h. Water (50 mL), ethyl acetate (50 mL), and brine (150 mL) were added and the organic phase was separated. The separated organic layer was dried and concentrated to yield a crude mixture as an oil (4.8 g) showing 4 components on examination by TLC [ethyl acetate:petroleum ether (3:1)] with R_f 0.9, 0.68, 0.6 and 0.35. The fastest moving component (R_f 0.9) and the slowest moving component (R_f 0.35) were readily separated by column chromatography in the same solvent system to yield firstly as an oil, an inseparable, approximately 1:1 mixture (R_f 0.9) of *cis*- and *trans*- isomers of methyl (4*RS*)-3-benzyl-2-phenyloxazolidine-4-carboxylate **25a** and **25b**, respectively (0.26 g, 2.5%), (Found: C, 72.6; H, 6.3; N, 5.1. $C_{18}H_{19}NO_3$ requires C, 72.7; H, 6.4; N, 4.7%); $\nu_{max.}$(film)/cm^{-1} no absorption at 3600-3100 (NH and OH), 1745 (CO); δ_H (60 MHz; $CDCl_3$; mixture of diastereomers) 3.52 and 3.76 (total 3 H, 2 s, 2 x OMe), 3.64-4.60 (5 H, complex, 4-H, 5-H_2, CH_2Ph), 5.20 and 5.60 (total 1 H, 2 s, 2 x C*H*Ph), 7.20-7.80 (10 H, complex, 2 x Ph).

The components R_f 0.68 and R_f 0.6 (< 0.2 g, in total) were not investigated further since their infrared and ^{1}H NMR spectra suggested they were not derived from serine.

Isolation of the slowest moving component (R_f 0.35) afforded as an oil, compound **34** (2.2 g, 21%), (Found: C, 62.5; H, 7.4; N, 7.0. $C_{11}H_{15}NO_3$ requires C, 63.1; H, 7.2; N, 6.7%); $\nu_{max.}$(film)/cm^{-1} 3600-3100 (br, OH and NH), 1740 (CO); δ_H (60 MHz; $CDCl_3$) 2.40 (2 H, br s, NH and OH), 3.28-4.16 (5 H, complex, CH, CH_2 and CH_2Ph), 3.76 (3 H, s, OMe), 7.36 (5 H, m, Ph).

N-*(*t-*Butyloxycarbonyl)*-DL-*serine Methyl Ester* **20**.— The procedure followed is essentially that described for preparation of the L- isomer.[5] To a stirred suspension of DL-serine methyl ester hydrochloride DL-**18** ·HCl (5.0 g, 32.1 mmol) at 0°C in THF (100 mL) containing triethylamine (9.6 mL, 78.3 mmol) was added a solution of di-*t*-butyl dicarbonate (7.2 g, 33.0 mmol) in THF (50 mL) over a period of 30 min. The mixture was allowed to warm to room temperature and was stirred at this temperature overnight, then was heated to

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60°C and stirred for a further 2 h. The solvent was removed and the resultant mixture was partitioned between diethyl ether (100 mL) and water (100 mL). The aqueous phase was extracted with further diethyl ether (2 x 50 mL) and the combined organic phases washed with aqueous hydrochloric acid solution (0.3 M, 80 mL), aqueous sodium hydrogen carbonate solution (0.5 M, 80 mL) and finally with brine (100 mL). On concentration the dried organic phase gave a crude oil (3.9 g) which on examination by TLC [ethyl acetate:petroleum ether (1:1)] was shown to contain a major component (R_f 0.35). Purification by column chromatography with the same solvent system gave as an oil compound **20** (2.5 g, 36%), (Found: C, 49.1; H, 7.9; N, 6.1. $C_9H_{17}NO_5$ requires C, 49.3; H, 7.8; N, 6.4%); $\nu_{max.}$(film)/cm^{-1} 3400 (br, OH and NH), 1745 (br, OCO), 1709 (NHCO); δ_H (60 MHz; $CDCl_3$) 1.48 (9 H, s, CMe_3), 2.76 (1 H, br s, OH), 3.80 (3 H, s, OMe), 3.72-4.16 (2 H, m, CH_2O), 4.16-4.60 (1 H, m, CHN), 5.36-5.76 (1 H, br d, NH).

*3-(1,1-Dimethylethyl) 4-Methyl (4*RS*)-2,2-Dimethyloxazolidine-3,4-dicarboxylate* **23**.— To a solution of compound **20** (2.0 g, 9.1 mmol) in a mixture of acetone (35 mL) and 2,2-dimethoxypropane (DMP) (10 mL) was added added boron trifluoride diethyl etherate (0.1 mL, 0.6 mmol) and the mixture was stirred for 2 h at room temperature. The solvent was then removed under reduced pressure, the resultant oil taken up into dichloromethane (30 mL) and this solution was washed with a mixture of water and saturated aqueous sodium hydrogen carbonate solution (20 mL, 1:1, v/v) and then with brine (30 mL). The organic phase was dried and concentrated to yield as an oil, acetal **23** (2.0 g, 85%), (R_f 0.65 in ethyl acetate); $\nu_{max.}$(film)/cm^{-1} 1760 (O-CO-O), 1710 (CO_2Me), no absorption near 3500; δ_H (60 MHz; $CDCl_3$; mixture of rotamers) 1.44, 1.52, 1.56 and 1.68 (15 H, 4 s, CMe_2 and CMe_3), 3.80 (3 H, s, OMe), 4.00-4.80 (5 H,¶ complex, NCH, OCH_2 and unknown -H).

¶ Curiously, the absorption for this unpurified material in the region for NCH and OCH_2 integrated for more than the expected 3-protons. This anomaly was also observed in an authentic sample provided by R. Watson at UEA. The crude material was utilised without further purification.

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*(1,1-Dimethylethyl) (4*RS*)-4-Hydroxymethyl-2,2-dimethyloxazoline-3-carboxylate* **33**.— A solution of **23** (1.9 g, 7.3 mmol) in ethanol (8 mL) was mixed with an ice-cold suspension of fine powdered calcium chloride (1.2 g, 10.8 mmol) and sodium borohydride (0.82 g, 21.7 mmol) in THF (8 mL) and the mixture was stirred at 0°C overnight. The resultant suspension was poured onto a mixture of crushed ice (100 g) and hydrochloric acid (1M, 100 mL) and extracted with diethyl ether (3 x 40 mL). The combined organic phases were washed with brine (50 mL) and the dried organic phase was concentrated to afford as an oil, a crude oil (1.5 g) (R_f 0.4 in ethyl acetate).¥ Column chromatography in the same solvent system gave the crystalline product **33** (1.26 g, 71%), m.p. 52-53.6˚C (Found: C, 57.4; H, 9.2; N, 5.7%. $C_{11}H_{21}NO_4$ requires C, 57.1; H, 9.15; N, 6.1%); $\nu_{max.}$(Nujol)/cm^{-1} 3470 (OH), 1670 (CO), 1370 and 1360 (CMe_2); δ_H (60 MHz; $CDCl_3$; mixture of rotamers) 1.48 and 1.56 (total 15 H, 2 s, CMe_2 and CMe_3), 3.60-4.60 (5 H, complex, $ROCH_2$, NCH, HOC*H*$_2$), 6.04 (1 H, br s, OH).

¥ Compound **10** was detected with ninhydrin

N-*Benzyloxycarbonyl*-DL-*serine Methyl Ester* **19**.— The procedure followed was that reported by Hassal and Thomas.[6] To a stirred solution of DL-serine methyl ester hydrochloride DL-**18** ·HCl (11.58 g, 74.5 mmol) in saturated aqueous sodium hydrogen carbonate solution (210 mL) was added benzyloxycarbonyl chloride (11.2 mL, 78.3 mmol) dropwise and the resultant emulsion was stirred vigorously for 3 h at room temperature. The mixture was then extracted with ethyl acetate (200 mL). Pyridine (0.1 mL) was added to the organic extract, which was sequentially washed with hydrochloric acid (0.1 M, 100 mL), sodium hydrogen carbonate solution (0.5 M, 100 mL) and finally with water until the latter was pH 7. The organic phase was dried, concentrated to yield a colourless syrup (18.91 g) (R_f 0.65 in ethyl acetate) which was washed with *n*-pentane (3 x 40 mL) by decantation. Further

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n-pentane (50 mL) and diethyl ether (0.5 mL) were added to the organic phase. The mixture was stored overnight at 4˚C to yield the crystalline derivative **19** (17.63 g, 91%), m.p. 32.5-35.3°C (Found: C, 57.1; H, 5.9; N, 5.4. $C_{12}H_{15}NO_5$ requires C, 56.9; H, 6.0; N, 5.5%); $\nu_{max.}$(Nujol)/cm^{-1} 3190 (br, OH and NH), 1755 (OCOMe), 1678 (NHCO), 1500, 1021, 916, 846, 732, 700; δ_H (90 MHz; $CDCl_3$) 3.36 (1 H, s, OH)¶, 3.69 (3 H, s, OMe), 3.86 (2 H, m, *J* 3.4, *CH*$_2$OH), 4.39 (1 H, m, CH), 5.08 (2 H, s, CH_2Ph), 6.04 (1 H, d, *J* 8.0, NH)¶, 7.3 (5 H, s, Ar-H); δ_C (22.6 MHz; $CDCl_3$) 52.39 (Me), 56.05 (CH), 62.64 (CH_2OH), 66.97 (CH_2Ph), 127.83, 127.97, 128.31 (Ar-C), 135.96 (Ar-C, C-1), 156.21 (*C*O_2CH_2Ph), 171.06 (*C*O_2Me).

¶ This signal disappeared on exchange with D_2O

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*3-Benzyl-4-methyl (4*RS)*-2,2-Dimethyloxazolidine-3,4-dicarboxylate* **22**.— This procedure follows the previous work of Pandit and co-workers.[7] To a solution of **19** (14.52 g, 57.3 mmol) in toluene (250 mL) was added *p*-toluenesulfonic acid monohydrate (250 mg, 1.3 mmol) and DMP (20 mL, 0.163 mol). The mixture was maintained under reflux with a Dean-Stark trap for 1 h. After cooling, the solution was concentrated to half of the previous volume, then diethyl ether (100 mL) was added. The organic solution was washed with saturated sodium hydrogen carbonate solution (2 x 50 mL), water (2 x 25 mL) and brine (2 x 25 mL). The dried solution was concentrated to afford a dark oil (15.61 g) containing the required product [R_f 0.84 in hexane:ethyl acetate (6:1)] which was isolated by column chromatography in the same solvent system to yield, as a yellow oil, compound **22** (14.12 g, 84%), (Found: C, 61.5; H, 6.5; N, 4.9. $C_{15}H_{19}NO_5$ requires C, 61.4; H, 6.5; N, 4.8%); $\nu_{max.}$(film)/cm^{-1} 1756 (OCOMe), 1714 (NCO), 1409, 1381 (CMe_2), 1352, 1208, 1095, 839, 766, 699; δ_H (90 MHz; $CDCl_3$; mixture of rotamers) 1.50 and 1.57 (3 H, s, *Me*CMe), 1.64 and 1.71 (3 H, s, MeC*Me*), 3.63 and 3.76 (3 H, s, OMe), 4.09-4.26 (2 H, m, CH_2O), 4.40-4.70 (1 H, complex, CH), 5.08-

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5.19 (2 H, m, OC*H*$_2$Ph), 7.31-7.55 (5 H, m, Ar-H); δ_C (22.6 MHz; $CDCl_3$; mixture of rotamers) 24.17 and 24.95 (*Me*CMe), 25.20 and 26.08 (MeC*Me)*, 52.4 (OMe), 58.94 and 59.63 (CHN), 66.21 and 66.59 (CH_2O), 66.79 and 67.52 (O*C*H_2Ph), 95.51 (CMe_2) 127.79, 128.01, 128.47 (Ar-*C*), 136.38 (Ar-C, C-1), 151.81 (*C*O_2CH_2Ph), 171.21 (*C*O_2Me).

Benzyl (*4*RS)*-4-Hydroxymethyl-2,2-dimethyloxazolidine-3-carboxylate* **30**.— A solution of **22** (10.75 g, 36.6 mmol) in ethanol (40 mL) was mixed with an ice-cold suspension of fine powdered calcium chloride (6 g, 54.0 mmol) and sodium borohydride (4.1 g, 0.108 mol) in dry THF (40 mL) and the mixture stirred at 0°C for 3 h. The suspension was then poured onto a mixture of crushed ice (50 g) and saturated ammonium chloride solution (50 mL) and ethyl acetate (100 mL) was added. The mixture was stirred for 30 min and concentrated hydrochloric acid (25 mL) was added dropwise. The phases were separated and then the aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed successively with saturated sodium hydrogen carbonate solution (50 mL), water (50 mL) and brine (50 mL). The dried organic phase containing the required alcohol [R_f 0.35, in light petroleum-ethyl acetate (2:1)] was concentrated to afford, as an oil, the alcohol **30** (9.19 g, 95%), (Found: C, 63.1; H, 7.2; N, 5.2. $C_{14}H_{19}NO_4$ requires C, 63.4; H, 7.2; N, 5.3%); $\nu_{max.}$(film)/cm^{-1} 3456 (br, OH), 1700 (NCO), 1412, 1380 (CMe_2), 1353, 1072, 841, 696; δ_H (90 MHz; $CDCl_3$; mixture of rotamers) 1.49 (3 H, br s, *Me*CMe) 1.56 (3 H, br s, MeC*Me*), 2.4-2.8 (1 H, br, OH), 3.66-3.99 (5 H, complex, C*H*$_2$OH and CHN, CH_2O), 5.14 (2 H, s, OC*H*$_2$Ph), 7.34 (5 H, br s, Ar-H); δ_C (22.6 MHz; $CDCl_3$; mixture of rotamers) 24.71-27.22 (C*Me*$_2$), 59.64-63.01 (CHN), 63.27-63.88 (CH_2O), 65.46 (CH_2OH), 67.02-67.65 (O*C*H_2Ph), 128.06, 128.24, 128.63 (Ar-C).¶

¶ The aromatic carbon C -1 and C=O could not be observed

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*Benzyl (4*RS*)-2,2-Dimethyl-4-(*p-*toluenesulfonyl) oxymethyloxazolidine-3-carboxylate* **31**.—To a cooled (0°C) and stirred solution of **30** (9 g, 33.9 mmol) in dichloromethane (50 mL) was added 4-(dimethylamino)pyridine (350 mg, 2.9 mmol) and pyridine (5 mL). *p*-Toluenesulfonyl chloride (7 g, 36.7 mmol) was added over 2 h at 0°C and the reaction mixture was then stirred for a further 24 h at room temperature. The reaction mixture was diluted with diethyl ether (150 mL) and washed with hydrochloric acid (1 M, 50 mL and 2 x 25 mL), saturated aqueous sodium hydrogen carbonate solution (25 mL), water (25 mL) and finally with brine (25 mL). The separated organic phase was dried and concentrated to give a crude oil containing the tosylate [R_f 0.4 in hexane:ethyl acetate (3:1)] which was purified by column chromatography in the same solvent system to afford as an oil, compound **30** (13.23 g, 93%), (Found: C, 60.3; H, 6.0; N, 3.2. $C_{21}H_{25}NO_6S$ requires C, 60.1; H, 6.0; N, 3.3%); $\nu_{max.}$(film)/cm^{-1} 1710 (NCO), 1456, 1358, 1261, 1178 (SO_2-O), 980, 816, 699; δ_H (90 MHz; $CDCl_3$; mixture of rotamers, peak broadening) 1.48 and 1.52 (6 H, 2br s, *Me*C*Me*), 2.43 (3 H, s, Ar*Me*), 3.80-4.32 (5 H, complex, C*H*$_2$OSO$_2$Ar, CHN and CH$_2$O), 5.08 (2 H, s, OC*H*$_2$Ph), 7.20-7.90 (4 H, m, AA'BB' system of Me*C*$_6$*H*$_4$SO$_2$), 7.34 (5 H, br s, C$_6$H$_5$); δ_C (22.6 MHz; $CDCl_3$; mixture of rotamers) 21.65 (Ar*Me*), 23.02 and 26.60 (C*Me*$_2$), 55.40 (CHN), 65.07 and 67.13 (*C*H$_2$OCMe$_2$ and *C*H$_2$OSO$_2$Ar), 67.67 (O*C*H$_2$Ph), 94.64 (*C*Me$_2$), 127.93, 128.03, 128.24, 128.62, 129.94, 132.90, 136.10, 144.98 (Ar-C), 155.36 (*C*O$_2$CH$_2$Ph).

*Benzyl (4*RS*)-4-(Azidomethyl) - 2,2 -dimethyloxazolidine-3-carboxylate* **32**.—To a stirred solution of **31** (6 g, 14.3 mmol) in *N,N* -dimethylformamide (50 mL) was added sodium azide (1 g, 15.4 mmol) and the solution was then heated for 6 h at 100°C. After removal of the solvent under reduced pressure the reaction mixture was distributed between dichloromethane (50 mL) and water (50 mL). The organic phase was separated, the aqueous phase extracted with dichloromethane (3 x 50 mL), and the combined organic phases were washed with water (3 x 50 mL), dried and then concentrated to give material (3.82 g) containing a major product

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[R_f 0.22 in hexane-ethyl acetate (5:1)]. Purification of this material by column chromatography in the same solvent system yielded, as a colourless oil, the azide **32** (3.48 g, 84%), (Found: C, 58.0; H, 6.3; N, 19.0. $C_{14}H_{18}N_4O_3$ requires C, 57.9; H, 6.25; N, 19.3%); $\nu_{max.}$(film)/cm^{-1} 2107 (N_3), 1700 (NCO), 1406, 1380 (CMe_2), 1351, 1260, 1070, 1029, 767, 698; δ_H (270 MHz; $CDCl_3$; mixture of rotamers) 1.46 and 1.56 (3 H, 2 s, *Me*CMe), 1.53 and 1.63 (3 H, 2 s, MeC*Me*), 3.20-3.65 (2 H, complex, CH_2N_3), 3.90-4.15 (3 H, complex, CHN and CH_2O), 5.08-5.22 (2 H, m, OC*H*$_2$Ph), 7.36 (5 H, br s, Ar-H); δ_C (67.9 MHz; $CDCl_3$; mixture of rotamers) 22.98 and 26.49 (*Me*CMe), 24.47 and 27.21 (MeC*Me*), 51.03 and 52.04 (CH_2N_3), 56.10 and 56.93 (CHN), 65.37 and 65.77 (*C*H_2OCMe$_2$-), 66.90 and 67.46 (O*C*H_2Ph), 94.27 and 94.72 (CMe_2), 127.98, 128.25, 128.62 , 135.97 and 136.17 (Ar-C), 151.95 (*C*O_2CH_2Ph).

*(2*RS*)-2,3-Diaminopropan-1-ol Dihydrochloride* **2** ·2 HCl.— A solution of **32** (2.9 g, 10 mmol) in a mixture of concentrated hydrochloric acid (3 mL) and ethanol (97 mL) was stirred under a slight overpressure of hydrogen in the presence of 10% palladium-charcoal (0.3 mg) for 24 h. The suspension was filtered through kieselguhr and the filtrate concentrated to yield crude crystalline material (0.22 g). The kieselguhr was washed with methanol (3 x 30 mL) and the combined filtrates were concentrated to yield a further amount of crystalline material (1.13 g). Recrystallisation of this combined crude material from methanol gave the dihydrochloride, **2** ·2 HCl (1.08 g, 66%), m.p. 176-178°C (lit.,[8] 172-174˚C) (Found: C, 22.15; H, 7.4; N, 16.85; Cl, 43.9. $C_3H_{12}N_2OCl_2$ requires C, 22.1; H, 7.4; N, 17.2; Cl, 43.5%); $\nu_{max.}$(Nujol)/cm^{-1} 3311 and 3214 (NH and OH), 1585, 1494, 1289, 1143, 1093, 1052, 715; δ_H (270 MHz; CD_3OD) 3.23-3.40 (2 H, m, 3-H_2), 3.59-3.68 (1 H, m, 2-H), 3.83 (1 H, dd, $J_{1,2}$ 4.5, $J_{1,1'}$ 11.72, 1-H), 3.87 (1 H, dd, $J_{1',2}$ 4.5, 1'-H); δ_C (67.9 MHz; CD_3OD) 40.60 (C-3), 52.21 (C-2), 61.01 (C-1).

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N-*Benzyloxycarbonyl*-L-*Serine Methyl Ester* **19c**.— Benzyloxycarbonyl chloride (14 mL, 98.1 mmol) was added dropwise to a stirred solution of L-serine methyl ester hydrochloride L-**18** ·HCl (15 g, 96.5 mmol) in saturated aqueous sodium hydrogen carbonate (250 mL) and the resultant emulsion was stirred vigorously for 4 h at room temperature. After extraction with ethyl acetate (300 mL), pyridine (0.1 mL) was added to the organic extract which was sequentially washed with hydrochloric acid (0.1 M, 100 mL), sodium hydrogen carbonate solution (0.5 M, 100 mL) and finally with water until washings were pH 7. The organic phase was dried and concentrated to yield a colourless syrup (23.23 g) (R_f 0.65 in ethyl acetate) which was then washed with *n*-pentane (3 x 50 mL) by decantation. Further *n*-pentane (50 mL) and diethyl ether (0.5 mL) were added to the organic phase. The mixture was stored overnight at 4°C to yield the crystalline derivative **19c** (22.9 g, 93%), m.p. 28-30°C (lit.,[6] 33-35°C), (Found: C, 56.5; H, 5.8, N, 5.3. $C_{12}H_{15}NO_5$ requires C, 56.9; H, 6.0; N, 5.5%); $[\alpha]_D$ -14.2° (*c* 1.0 in MeOH) {lit.,[6] $[\alpha]_D$-13.2° (*c* 10.0 in MeOH); lit.,[7] $[\alpha]_D$ (syrup) -12.5° (*c* 1.0 in MeOH)}.¶

¶ Spectroscopic data for **19c** are identical to corresponding data for the racemic compound **19**.

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*3 - Benzyl - 4 - methyl (4*S*) -2 ,2 -Dimethyloxazolidine -3 ,4 - dicarboxylate* **22c**.— DMP (20 mL, 0.163 mol) and *p*-toluenesulfonic acid monohydrate (250 mg, 1.3 mmol) were added to a solution of **19c** (14.52 g, 57.3 mmol) in toluene (250 mL). The mixture was maintained under reflux with a Dean-Stark trap for 1 h. The solution was then cooled, concentrated to half of the previous volume and diethyl ether (100 mL) was then added. The organic solution was washed with saturated sodium hydrogen carbonate solution (2 x 50 mL), water (2 x 50 mL) and brine (2 x 50 mL) and the dried solution was concentrated to afford a dark oil (14.44 g) of the crude product which was purified by column chromatography

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[hexane:ethyl acetate (6:1)]. Purification gave as a yellow oil (R_f 0.85, same solvent system), the compound **22c** (13.75 g, 82%), (Found: C, 61.5; H, 6.4; N, 4.8. $C_{15}H_{19}NO_5$ requires C, 61.4; H, 6.5; N, 4.8%); $[\alpha]_D$ -54.95° (*c* 2.0 in CH_2Cl_2) {lit.,[7] $[\alpha]_D$ -49.5° (*c* 2 in CH_2Cl_2)}.¥

¥ Spectroscopic data for **22c** are identical to corresponding data for the racemic compound **22**.

*Benzyl (4*R*)-4-Hydroxymethyl-2,2-dimethyl-oxazolidine-3-carboxylate* **30c**.— A solution of **22c** (13 g, 44.4 mmol) in ethanol (45 mL) was added to an ice-cold suspension of fine powdered calcium chloride (7.38 g, 66.5 mmol) and sodium borohydride (5 g, 132.2 mmol) in dry THF (45 mL). The mixture was stirred at 0°C for 3 h, and the resultant suspension was then poured onto a mixture of crushed ice (50 g) and saturated ammonium chloride solution (80 mL). Ethyl acetate (50 mL) was then added. The mixture was stirred for 30 min and concentrated hydrochloric acid (25 mL) was then added dropwise. The phases were separated and the aqueous phase extracted with ethyl acetate (2 x 50 mL). The organic phases were combined and were then washed successively with saturated sodium hydrogen carbonate solution (50 mL), water (50 mL) and brine (50 mL). The organic solution was dried, concentrated, and purified by column chromatography [hexane-ethyl acetate (3:2)] to yield as an oil (R_f 0.8 in the same system), compound **30c** (9.76 g, 83%), (Found: C, 63.1; H, 7.3; N, 5.2. $C_{14}H_{19}NO_4$ requires C, 63.4; H, 7.2; N, 5.3%); $[\alpha]_D$ -19.1° (*c* 1.0 in CH_2Cl_2) {lit.,[7] $[\alpha]_D$-19.5° (*c* 1.0 in CH_2Cl_2) }.¶

¶ Spectroscopic data for **30c** are identical to corresponding data for the racemic compound **30**.

*Benzyl(4*S*)-2,2-Dimethyl-4-(*p*-toluenesulfonyloxymethyl)oxazolidine-3-carboxylate* **31c**.— 4-(Dimethylamino)pyridine (250 mg, 2.1 mmol) and pyridine (5 mL) were added to a cooled

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(0°C) and stirred solution of **30c** (4.82 g, 11.5 mmol) in dichloromethane (40 mL). *p*-Toluenesulfonyl chloride (6 g, 31.5 mmol) was then added over 2 h at 0°C and the reaction mixture was stirred for a further 24 h at room temperature. After dilution with diethyl ether (75 mL), the reaction mixture was washed with hydrochloric acid (1M, 3 x 25 mL), saturated aqueous sodium hydrogen carbonate solution (25 mL), water (25 mL) and brine (25 mL). The organic phase was dried and concentrated to give a crude oil (5.74 g) which crystallised on storage under high vacuum. Recrystallisation [ethyl acetate:petroleum ether (1:5)] gave the pure tosylate **31c** (5.23 g, 68.8%), m.p. 72-74°C (lit.,[7] 82-86°C) (Found: C, 60.1; H, 5.95; N, 3.3. $C_{21}H_{25}NO_6S$ requires C, 60.1; H, 6.0; N, 3.3%); $[\alpha]_D$ -43.6° (*c* 1.0, CH_2Cl_2) {lit.[7] -39.0° (*c* 1.0, CH_2Cl_2)}.¥

¥ Spectroscopic data for **31c** are identical to corresponding data for the racemic compound **31.**

*Benzyl (4*R*)-4-(Azidomethyl)- 2, 2 -dimethyloxazolidine-3-carboxylate* **32c**.—Sodium azide (0.7 g, 10.7 mmol) was added to a stirred solution of **31c** (4 g, 9.5 mmol) in *N,N* -dimethylformamide (50 mL) and the solution was then heated for 4 h at 100°C (oil bath). After removal of the solvent under reduced pressure the residue was distributed between dichloromethane (50 mL) and water (50 mL). The organic phase was separated, the aqueous layer extracted with dichloromethane (3 x 40 mL), and the combined organic phases were washed with water (3 x 50 mL), dried and concentrated to give an oil (2.51g). This was purified by column chromatography [hexane-ethyl acetate (5:1)] to give a major fraction (R_f 0.22), which on concentration gave, as an oil, the title compound **32c** (2.18g, 79%), (Found: C, 57.9; H, 6.2; N, 19.3. $C_{14}H_{18}N_4O_3$ requires C, 57.9; H, 6.25; N, 19.3%); $[\alpha]_D$ -33.9° (*c* 1 in $CHCl_3$).¶

¶ Spectroscopic data for **32c** are identical to corresponding data for the racemic compound **32**.

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*(*R*)-2,3-Diaminopropan-1-ol Dihydrochloride* **2c** ·2HCl.— A solution of **32c** (1 g, 3.4 mmol) in a mixture of concentrated hydrochloric acid and ethanol (1:99, v/v; 14 mL) was stirred under a slight overpressure of hydrogen in the presence of 10% palladium-charcoal (0.15 g) for 24 h. After removal of the catalyst by filtration through kieselguhr the solution was concentrated to yield crystalline material (0.1 g). The kieselguhr was washed with methanol (3 x 10 mL) and the combined filtrates were concentrated to yield a further amount of crystalline material (0.4 g). The combined crystals were recrystallised from methanol to give the dihydrochloride **2c** ·2HCl (0.5 g, 89%), m.p. 188-190°C (Found: C, 21.9, H, 7.4; N, 16.65; Cl, 42.6; $C_3H_{12}N_2OCl_2$ requires C, 22.1; H, 7.4; N, 17.2; Cl, 43.5%); $[\alpha]_D$ -13.3°,¥ $[\alpha]_{546}$ -15.8°; $[\alpha]_{435}$ -25.5° (*c* 1 in MeOH) and $[\alpha]_D$ -11.8°; $[\alpha]_{546}$ -13.7°; $[\alpha]_{435}$ -24.1°; $[\alpha]_{365}$ -39.2° (*c* 1.0 in H_2O); {lit.,[9] $[\alpha]_D$ -6.3° (*c* 1.0 in H_2O)}.¶

¥ An earlier measurement on the rotation of **2c** ·2HCl in methanol at a slightly higher concentration (*c* 1.4) gave an $[\alpha]_D$ value of -15.8°. At the moment we have no explanation for the difference in this value from that (-13.3°) measurement at the lower concentration (*c* 1 in MeOH) but it is unlikely to be a concentration effect.
¶ Spectroscopic data for **2c** ·2 HCl are identical to corresponding data for the racemic compound **2** ·2 HCl.

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M.Sc. Thesis

STUDIES TOWARDS THE SYNTHESIS OF PHOSPHATIDYLCHOLINE ANALOGUES

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Abstract

A new synthetic route towards the compound 2,3-diaminopropan-1-ol **2** was developed in order to provide the starting material for the synthesis of diamido analogues of phosphatidylcholine which show potential as anti-HIV agents. The diamino alcohol **2** was synthesised in both racemic and a chiral form starting from the amino acid and chiral building block serine. Serine was used as the readily available methyl ester hydrochloride in racemic form **18** ·HCl or as the L-enantiomer **18c** ·HCl.

Syntheses were investigated with a variety of different protecting groups, for example *t*-butyloxycarbonyl or benzyloxycarbonyl for *N*-protection coupled with *N, O*-protection by the isopropylidene group to give oxazolidine derivatives. As an alternative strategy, *N, O*-protection was achieved by reaction of **18** ·HCl and **18c** ·HCl with ethyl benzimidate to give 4,5-dihydrooxazole derivatives. The successful conversion of the ester group into the aminomethyl group was achieved with the oxazolidine derivatives in several steps to give, after removal of protecting groups, the required diamino alcohol **2**, in both racemic and one chiral form.

Fosfatidilkolin analoglarının sentezi üzerine çalışmalar

Özet

Anti-HIV etki potansiyeli gösteren diamino fosfatidilkolin analoglarını sentezlemek üzere baslangıç maddesi olan 2,3-diaminopropan-1-ol'e yönelik yeni bir yöntem geliştirildi. Bu diamino alkol rasemik ve şiral olarak serin amino asitinden hareketle sentezlendi. Serin, hazır olarak metil ester HCl tuzu halinde rasemik veya L-enantiyomeri halinde kullanıldı.

Değişik koruyucu gruplarla sentez yöntemleri araştırıldı. Örneğin, oksazolidin türevleri vermek üzere N-grubu koruyucusu t-butiloksikarbonil ya da benziloksikarbonil ve ardından N,O-grupları koruyucusu olarak izopropiliden grupları sentezlendi. Diğer bir yöntem olarak N, O-grupları koruyucusu DL-serin metil ester HCl tuzu ya da L-serin metil ester HCl tuzunun etil etilbenzimidat ile 4,5-dihidrooksazol türevleri sentezlendi. Oksazolidin türevlerinin ester gruplarının amino metil grubuna dönüştürülmesi ve koruyucu grupların uzaklaştırılması sonucu istenen diamino alkolün gerek rasemik gerekse şiral halde başarı ile sentezlenmiştir.