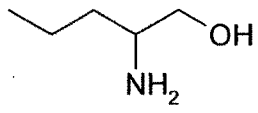
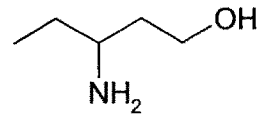
CHAPTER - I

INTRODUCTION

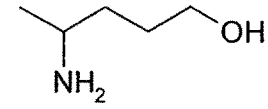
Amino alcohols are versatile molecules, due to the presence of functionalities such as amino and hydroxyl groups in a single molecule. This combination makes them useful for countless industrial applications such as textiles, household products and in pharmaceutical industries.[1] Depending upon the position of the hydroxyl and amino group, the amino alcohols may be classified accordingly as 1, 2; 1, 3; 1, 4-amino alcohols.



1, 2-amino alcohol



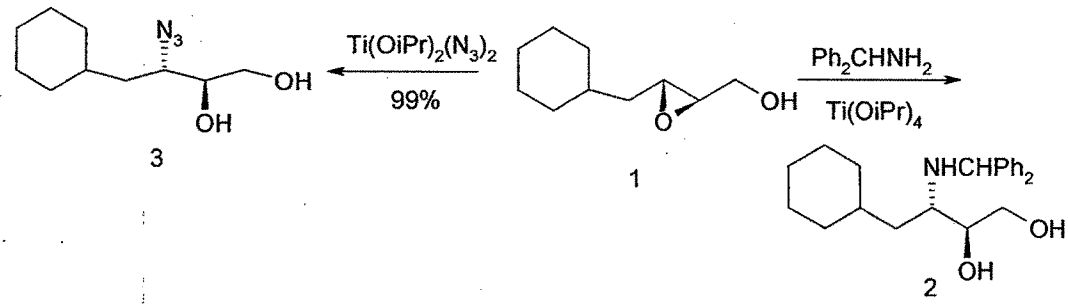
1, 3- amino alcohol



1, 4-amino alcohol

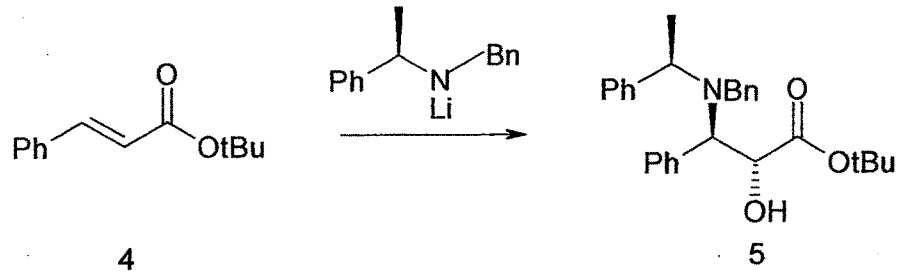
1.1 METHODS OF PREPARATION OF 1, 2-AMINO ALCOHOLS

Pasto *et al.*[2] have devised a stereospecific and regiosepecific method of synthesis of amino alcohol 2 and azido alcohol 3 by ring opening reaction of the epoxide 1 (**Scheme I.1**)



Scheme I.1

A method by Davies for synthesis of 5 is the addition of a chiral amide anion to and α, β-unsaturated ester 4 followed by trapping of the resulting enolate with the oxygen electrophile (**Scheme I.2**).[3]



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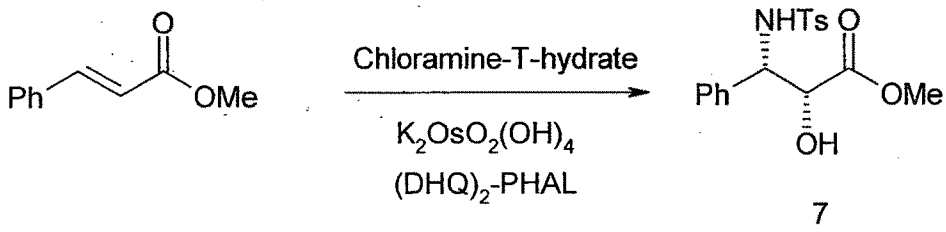
Scheme I.2

Another highly stereospecific synthesis of the amino alcohol 7 similar to the above method was established by Sharpless (**Scheme I.3**).[4]



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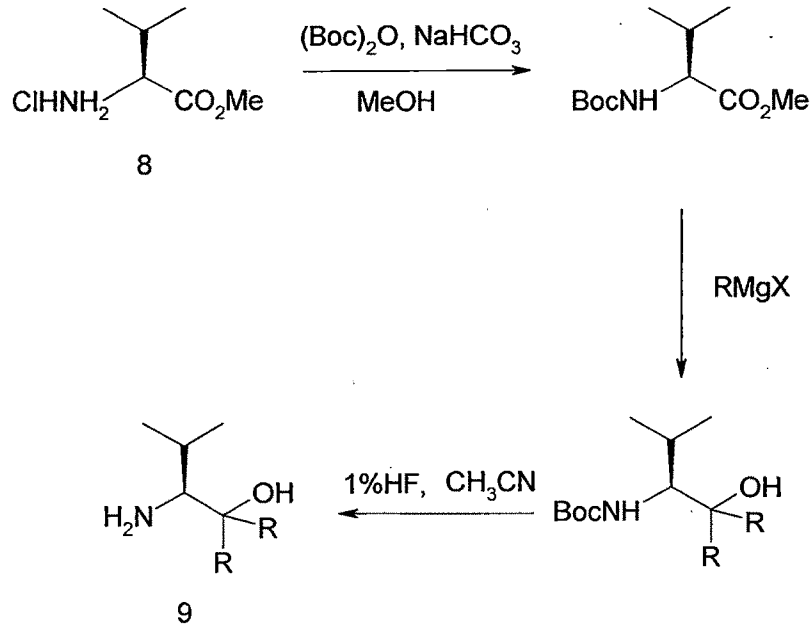
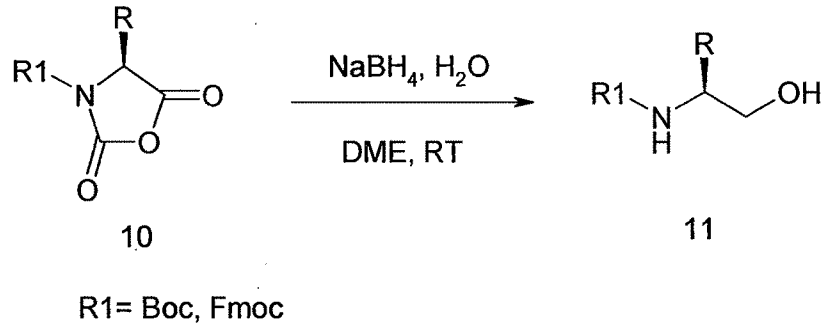
Scheme I.3

Uncommon β-amino alcohols 9 were obtained in high yields from N-Boc-L-valinate (8) and Grignard reagents (**Scheme I.4**).[5]



Scheme I.4

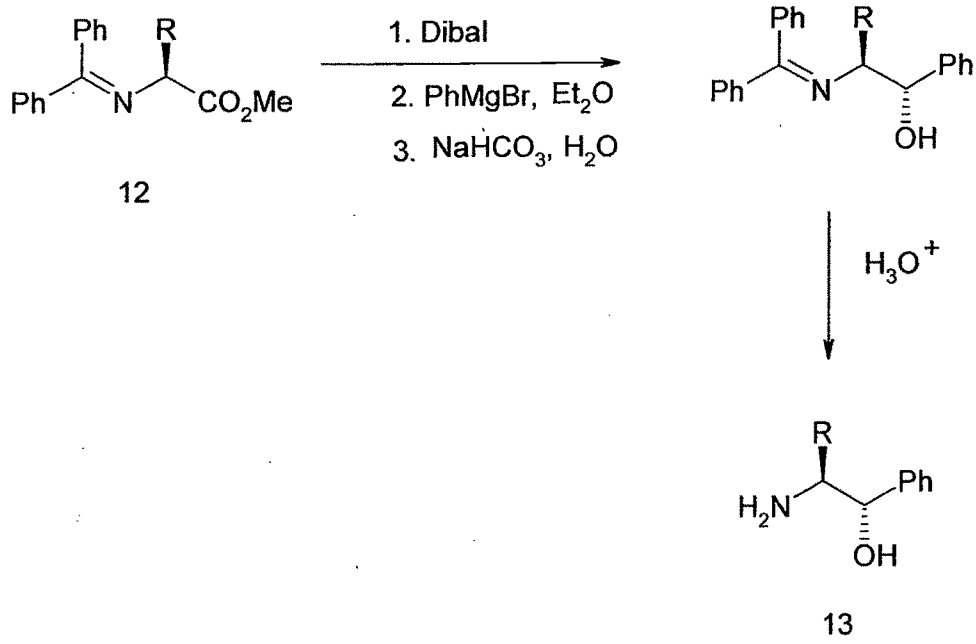
Sodium borohydride reduction of N-protected N-carboxyanhydrides 10 results in formation of the β-amino alcohols 11 (**Scheme I.5**).[6]



R1= Boc, Fmoc

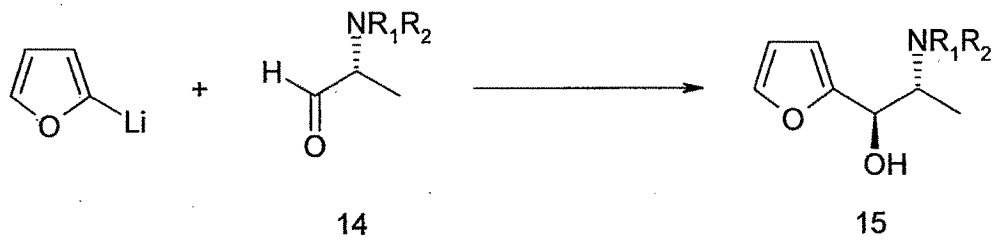
Scheme I.5

The imine 12 derived from benzophenone and a α-Amino ester has been converted into the corresponding amino alcohol 13 by reduction and subsequent reaction with an organometallic reagent (**Scheme I.6**).[7]



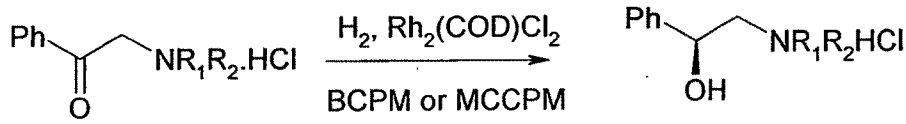
Scheme I.6

α-Amino aldehydes 14 undergo highly selective additions by furyl lithium reagent to give the amino alcohol 15 (**Scheme I.7**).[8]



Scheme I.7

α-Amino alcohols 16 are also synthesized by reduction of α-amino carbonyl compounds (**Scheme I.8**).[9]



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Scheme I.8

1.2 IMPORTANCE OF VICINAL AMINO ALCOHOLS

The 1, 2-aminoalcohol moieties, in the form of ethanolamine, choline or serine, is present as a structural sub-unit in glycerol subunit and sphingosine class of phosphatides. These compounds, which possess both lipophilic and hydrophilic groups that probably function as structural bridges between water-soluble protein and non-polar lipid, are implicated in a wide range of physiological processes in addition to their prime functions with respect to fat metabolism.

The phosphatide base choline also has separate roles as a methyl donor in the conversion of homocysteine to the essential amino acid methionine and a precursor of acetyl choline, the chemical mediator involved in certain nervous control mechanisms in the body such as parasympathetic pathways in the autonomic nervous system.

The 1, 2-aminoalcohol moieties is also present in two other physiologically important compounds, adrenaline and noradrenalin, the principal mediators of the sympathetic nervous system. The therapeutic significance of these catecholamines has long been recognized and Hartung[10] has provided a fascinating review of the discovery, preparation and early efforts to synthesize analogs of these substances.

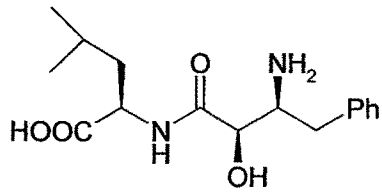
Two general groups of vicinal amino alcohols have been reported in literature

1.2.1 Naturally occurring molecules containing vicinal amino alcohols

1.2.2 Synthetic pharmacologically active molecules containing vicinal amino alcohols

1.2.1 Naturally Occuring Molecules

Hydroxy amino acids are one of the most common naturally occurring molecules that contain a vicinal amino alcohol. The naturally occurring amino alcohols serine and threonine are both biologically significant as well as being useful members of the chiral pool. Some of the well known examples are shown in **figure I.1**.



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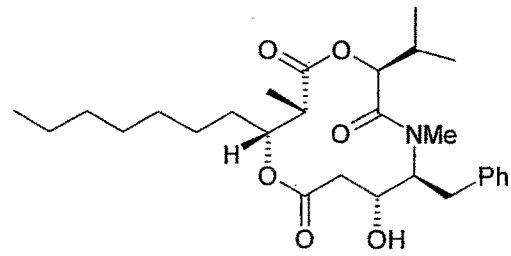

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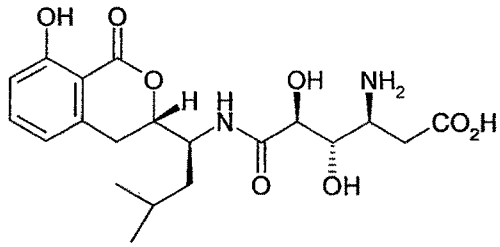

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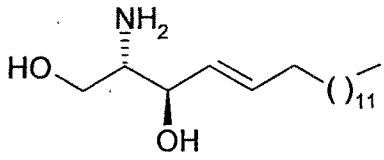
Figure I.1

The most synthesized of this group is the dipeptide bestatin (17). Bestatin is an amino peptidase inhibitor that exhibits immunodulatory activity[11, 12] and is used clinically as an adjuvant in cancer chemotherapy.[13] Hapalosin (18) has attracted considerable interest due to its ability to inhibit multidrug resistance MDR in drug resistant cancer cells.[14-17]

Another example of a vicinal amino alcohol containing amino acid is the lactone 40, which shows gastro protective activity.[18, 19]

Sphingosine (20) is found to be important in cell signaling.[20] Sulfobacin B (21) is an interesting sphingosine analog recently isolated[21] and is useful as an antithrombotic agent. Myriocin (22) is a potent immunostimulatory agent (**Figure I.2**).[22]



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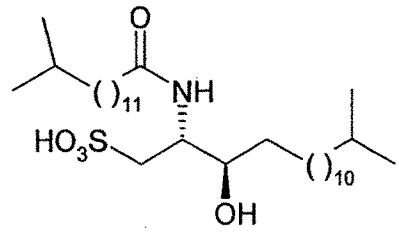

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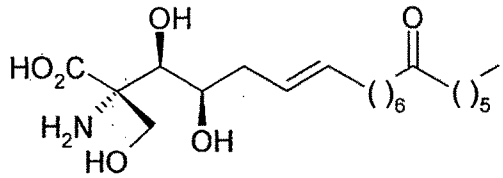

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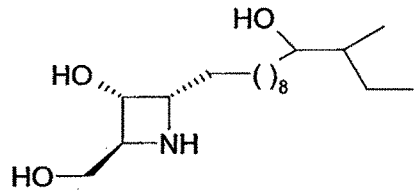
Figure I.2

Penaresidin A (23), an azetedine amino alcohol[23] is an actomyos ATPase activator. Anisomycin (24) obtained from the extracts of a streptomyces is a potent inhibitor in protein biosynthesis that may be useful as an anticancer agent.[24,25] Febrifugine (25) is a structurally unique amino alcohol in which the amino group is contained within a piperidine ring and is a useful antimalarial agent.[26] Another well known example is swainsonine (26), which is an inhibitor of glycoprotein processing **(Figure I.3).**[27]



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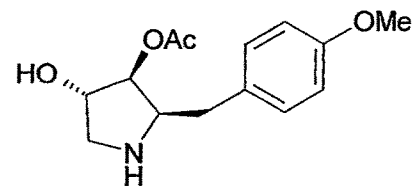

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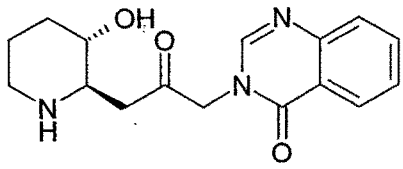

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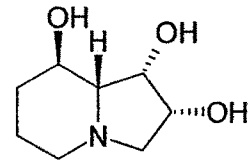

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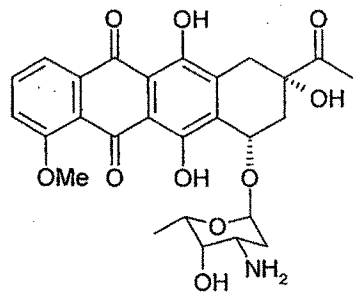
Figure I.3

Daunomycin (27) is a glycosylated anthracycline natural products.[28] ElsamycinA (28)[29] is an antitumour antibiotic in which the presence of the aminosugar, both enhances the biological activity and improves the water solubility of the antibiotic. These compounds are primarily used for the treatment of gram-negative and gram positive bacterial infection. **(Figure I.4).**



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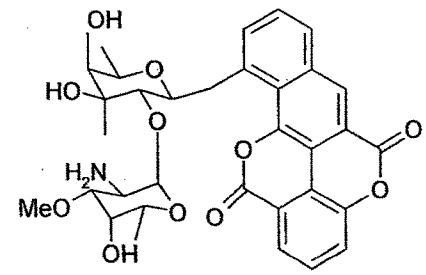

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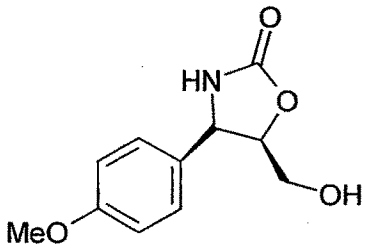
Figure I.4

Cytoxazone (29), in which the amino alcohol moiety is contained within an oxazolidinone ring[30] is reported to be an immunomodulator. Balanol (30), [31] an azepino amino alcohol has attracted considerable synthetic interest due to its ability to inhibit protein kinase.[32, 33] Aceropterine (31) is a structurally unique alkaloid from the Caribbean Sea plume psuedoptrogorgia acerosa which contain a vicinal amino alcohol.[34] **(Figure I.5)**



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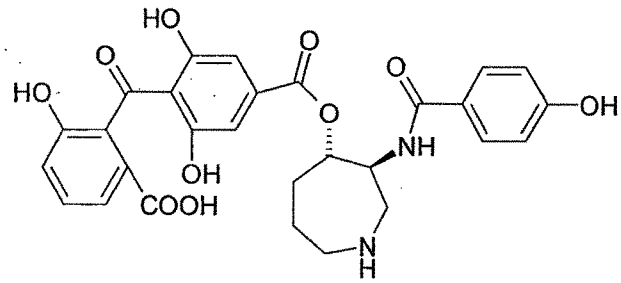

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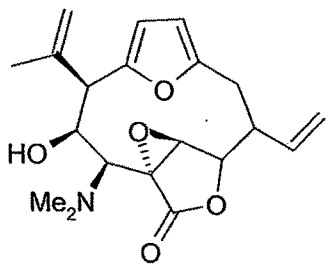

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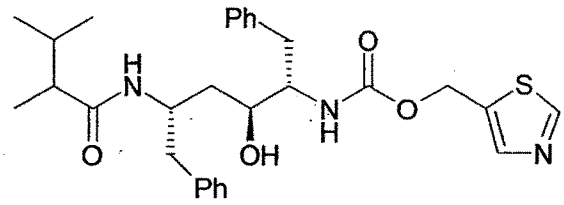
Figure I.5

1.2.2 Synthetic Pharmacologically Active Molecules

A host of synthetic molecules used as drugs or pharmacological agents also contain the vicinal amino alcohol moiety. This group of peptide analogs is typified by HIV protease inhibitor Saquinavir (32).[35] Molecules such as 33 which contain the vicinal amino alcohol are being investigated as anti HIV agents.[36] The amidine 34 is reported to be an inhibitor of nitric oxide synthetase (NOS) and has therapeutic implications for the treatment of a wide variety of disease states **(figure I.6)**.[37]

The presence of the vicinal amino alcohol moiety in the pharmacologically active molecules is essential for biological activity.



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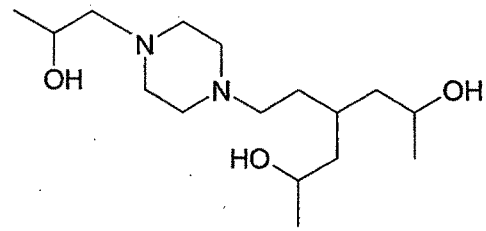

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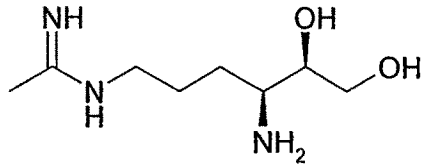

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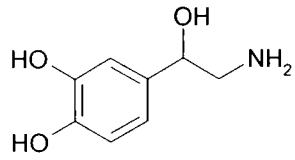
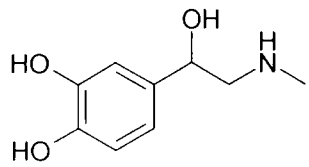
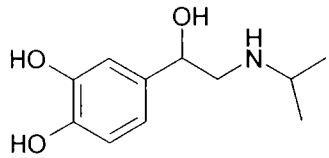
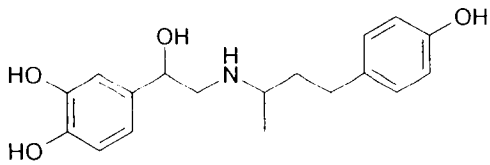
Figure I.6

1.3 ARYLETHANOLAMINES

Aryl ethanol amines are another important class of amino alcohols on which a lot of focus and attention has been paid in terms of its uses as potential drugs. Recent developments based on the chemical structure and activity relationship indicate several arylethanolamines which are used as potential drugs depending on their activation of α- and β- adrenergic receptors **(Table I.1).**

Drug	Main action	Uses/function
Noradrenaline  35	α/β-agonist	Not used clinically, trans-mitter at post ganglionic, sympathetic neurons and in CNS hormones of adrenal medulla
Adrenaline  36	α/β-agonist	asthma (emergency treatment) anaphylactic shock, cardiac arrest, Hormone of adrenal medulla.
Isoprenaline  37	Nonselective β-agonist	Asthma not as endogenous substance
Dobutamine  38	selective β_1-agonist	Used for treating cardiogenic shock

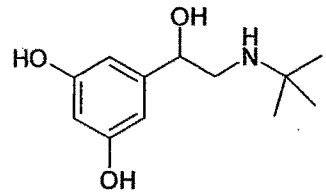
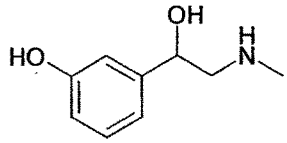
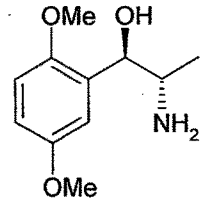
Terbutaline  39	selective β_2-agonist	Used for treatment of asthma
Phenyl ephedrine  40	selective α_1-agonist	Used for nasal decongestion
Methoxamine  41	nonselective α-agonist	Used for nasal decongestion

Table I.1 Representatives of important adrenoreceptor agonists of Sympathomimetic type (Direct acting)

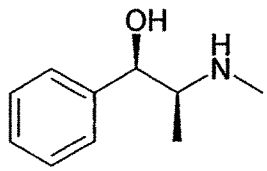
Drug	Main action	Uses/function
Ephedrine  42	noradrenergic release	Used in nasal decongestion

Table I.2 Representatives of indirectly acting Sympathomimetic arylethanolamines and their clinical uses

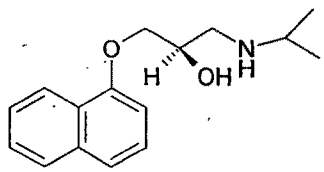
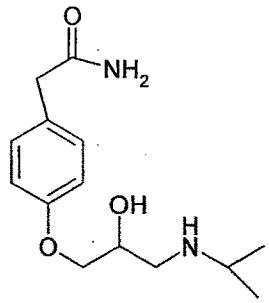
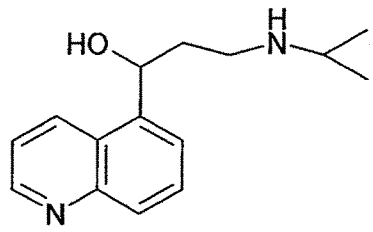
Drug	Main action	Uses/function
Propranolol  (R) 43	nonselective β -antagonist	vasoconstriction
Atenolol  44	Selective β_1 and β_2 antagonist	β -adrenergic blocker

Table I.3 Some important Adrenoceptor antagonists and their clinical use

The other types of arylethanolamines used as potent drugs are as follows:

Quinoprenaline (45) has bronchodilating, vasodilating, uterine relaxing activity. Tetrahydroquinolinol (46) has a much greater effect on cardiac muscles. Hence, it is used for treating mild asthma **(Figure I.7)**.



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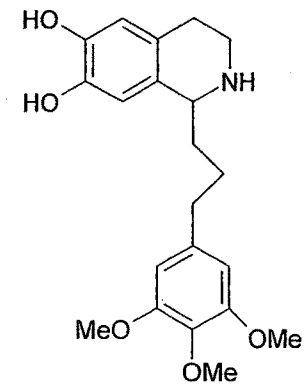

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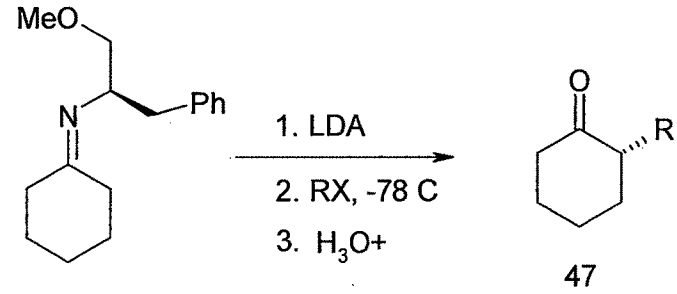
Figure I.7

1.4 USE OF AMINOALCOHOLS AS CHIRAL AUXILIARIES

Amino alcohols are extensively used as chiral auxiliaries generally as part of a cyclic system, especially five membered rings. However, acyclic amino alcohols have also been used as auxiliaries in asymmetric synthesis.

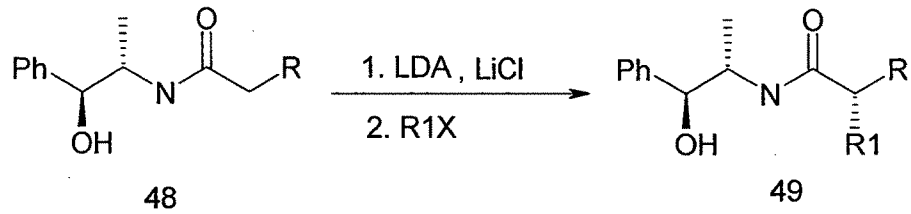
1.4.1 Acyclic 1, 2-Amino Alcohol Derivatives

The alkylation of cyclohexanone has been carried out with a great degree of stereo control using amino alcohol as a chiral auxiliary to obtain enantiomerically pure alkylated cyclohexanones 47 **(Scheme I.9)** .[38,39]



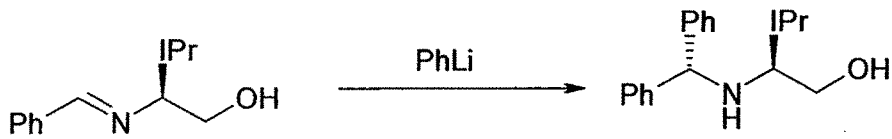
Scheme I.9

The amide derivatives 48 of psuedoephedrine are alkylated with great stereo control and hydrolysis of the amide products 49 results in highly enantiomerically enriched carboxylic acids **(Scheme I.10).**[40]



Scheme I.10

The reaction of 1, 2-amino alcohols with a carbonyl compound is reported to give an imine 50 which undergoes addition reaction with Grignard or organolithium reagent with a high degree of induction **(Scheme I.11).**[41]



50

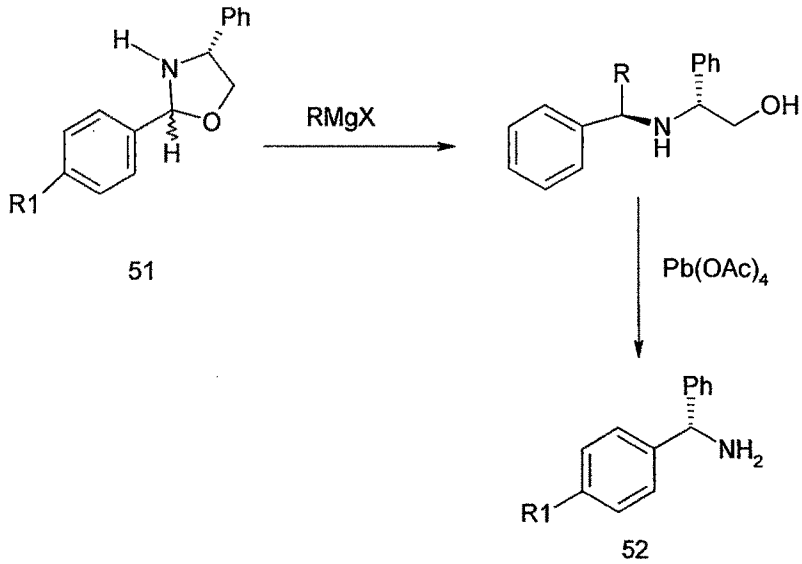
Scheme I.11

The degree of induction may be high; however the auxiliary is not trivial to remove. The problem has been solved by the use of a hydrazone derived from ephedrine; reduction of the N-N bond then removes the auxiliary.[42]

1.4.2 Cyclic Derivatives as Auxiliaries

a. Oxazolidines

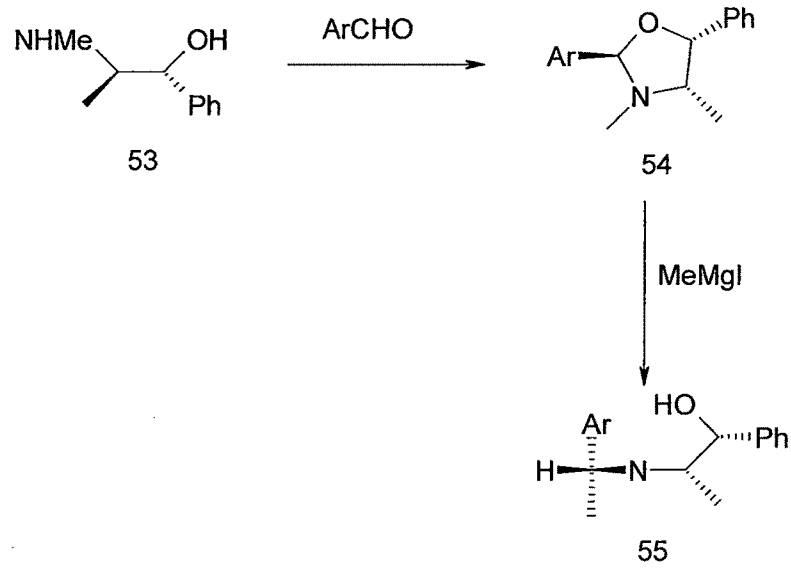
Oxazolidines (51) undergo Grignard addition and subsequent removal of the auxiliary results in the formation of the amine 52 with good induction **(Scheme I.12).**[43, 44]



51 52

Scheme I.12

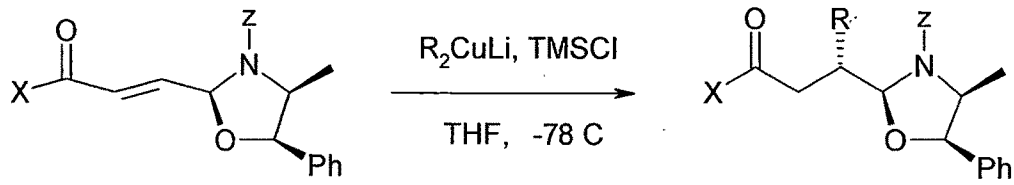
Reaction of ephedrine (53) with aromatic aldehyde forms an oxazolidine (54) that can be cleaved by addition of Grignard reagents to give tertiary amino alcohols 55 **(Scheme I.13).**[45, 46]



53 54 55

Scheme I.13

The oxazolidine (56) undergoes a 1, 4 addition of a cuprate to α, β-unsaturated carbonyl systems[47] **(Scheme I.14).**

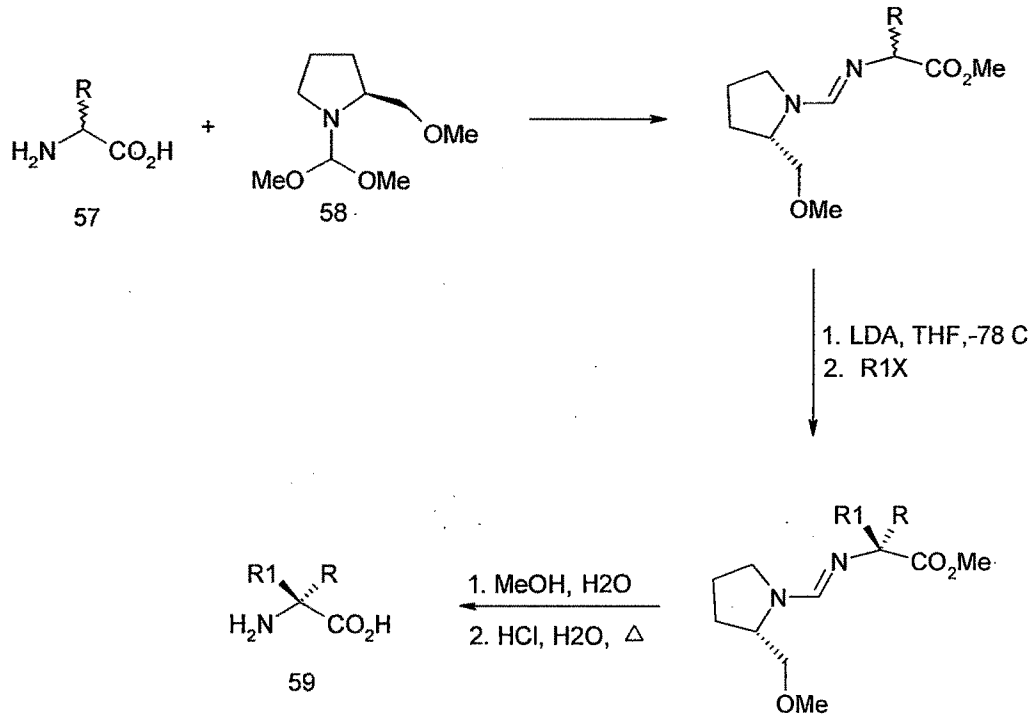


56

Scheme I.14

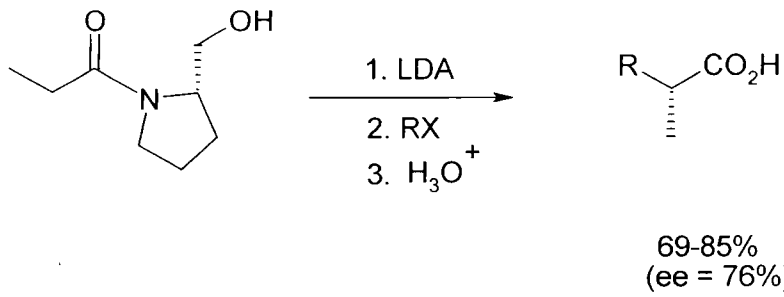
b. Proline derivatives

Racemic amino acids 57 can be alkylated with a high degree of enantioselectivity through the use of a proline derived acetal 58 to get enantiomerically pure amino acids 59 **(Scheme I.15).**[48]



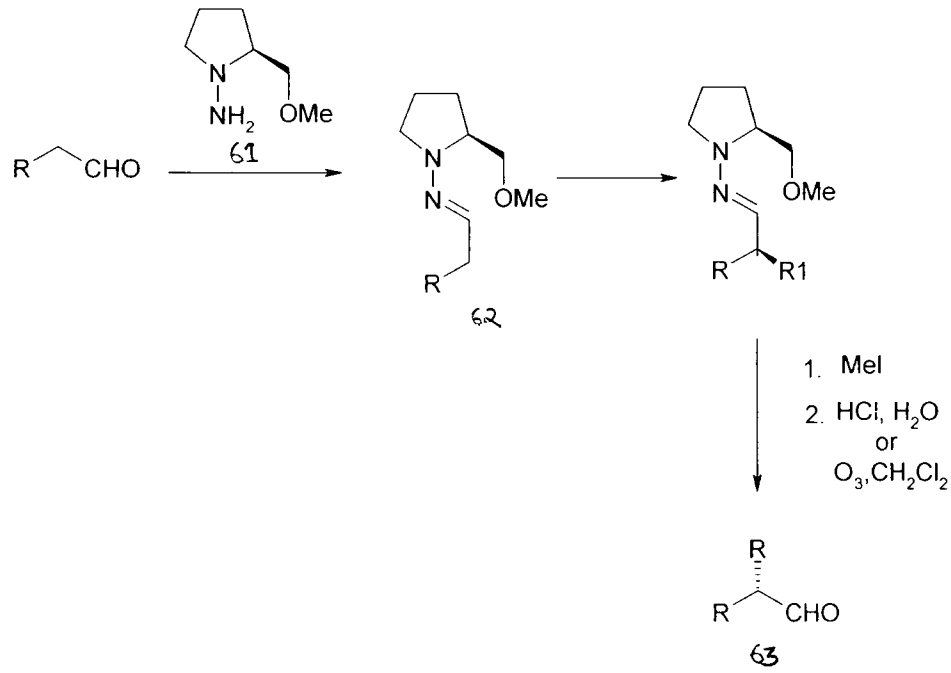
Scheme I.15

Proline derived amides (60) provide for reasonable degrees of diastereoselection in alkylation reaction **(Scheme I.16).**[49]



Scheme I.16

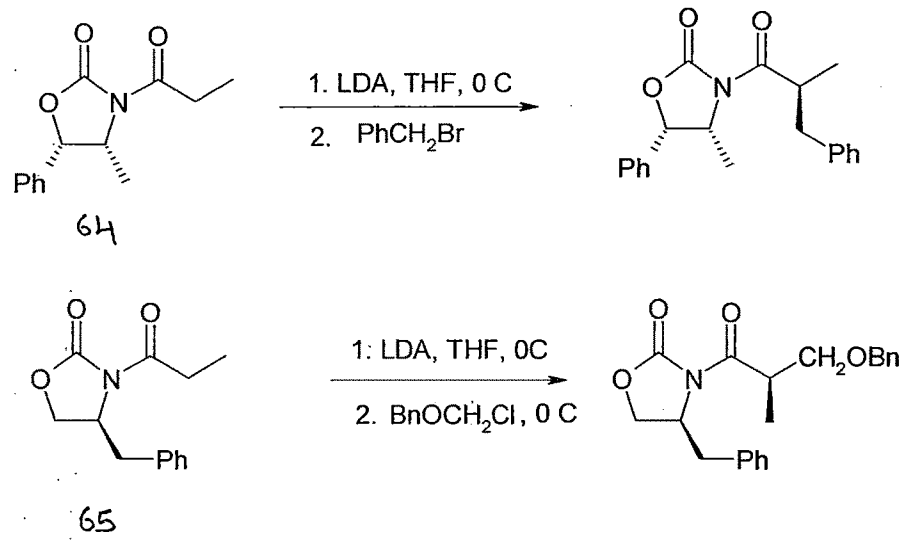
The hydrazone formed with by reaction of 61 with the aldehyde, subsequent deprotonation of the hydrazone 62 and alkylation provides the substituted hydrazone that can be converted into the aldehyde 63 by ozonolysis or hydrolysis of the methiodide **(Scheme I.17).**[50]



Scheme I.17

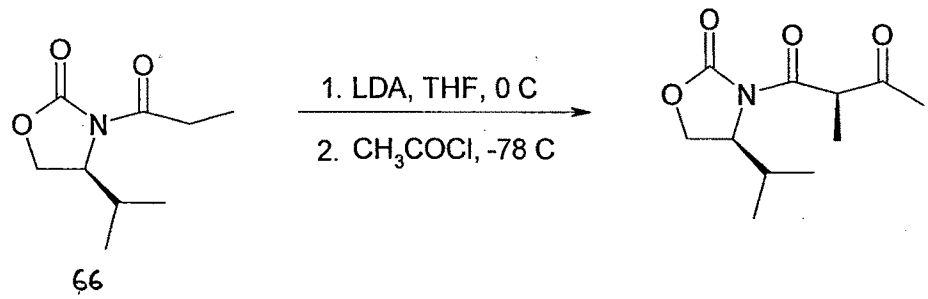
c. Oxazolidinones

Alkylation of N-acyloxazolidinones 64 and 65 are carried out with a high degree of diastereoselectivity **(Scheme I.18).**[51]



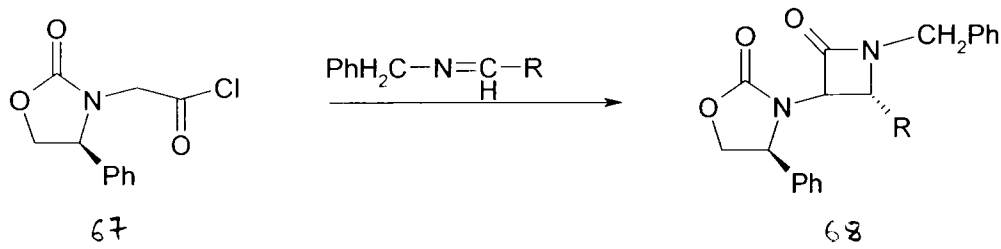
Scheme I.18

The chiral enolates of oxazolidinones 66 also undergo highly diastereoselective acylation reactions that give rise to chiral dicarbonyl synthons **(Scheme I.19).**[52]



Scheme I.19

The reaction of oxazolidinone 67 with N-benzylimines proceeds with an exceptional level of asymmetric induction to form the β-lactams 68 in good yields **(Scheme I.20).**[53]

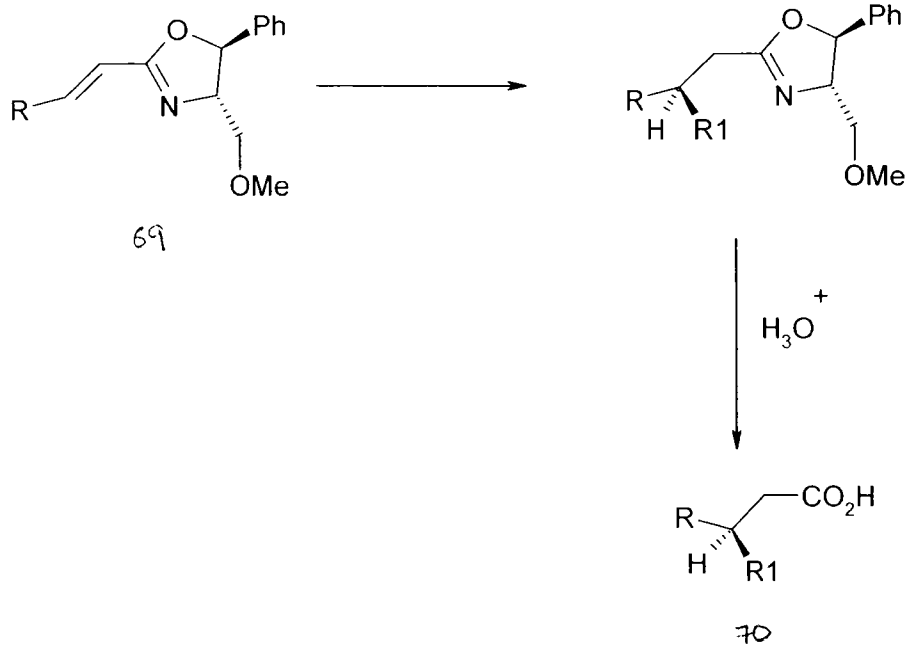


67 68

Scheme I.20

d. Oxazolines

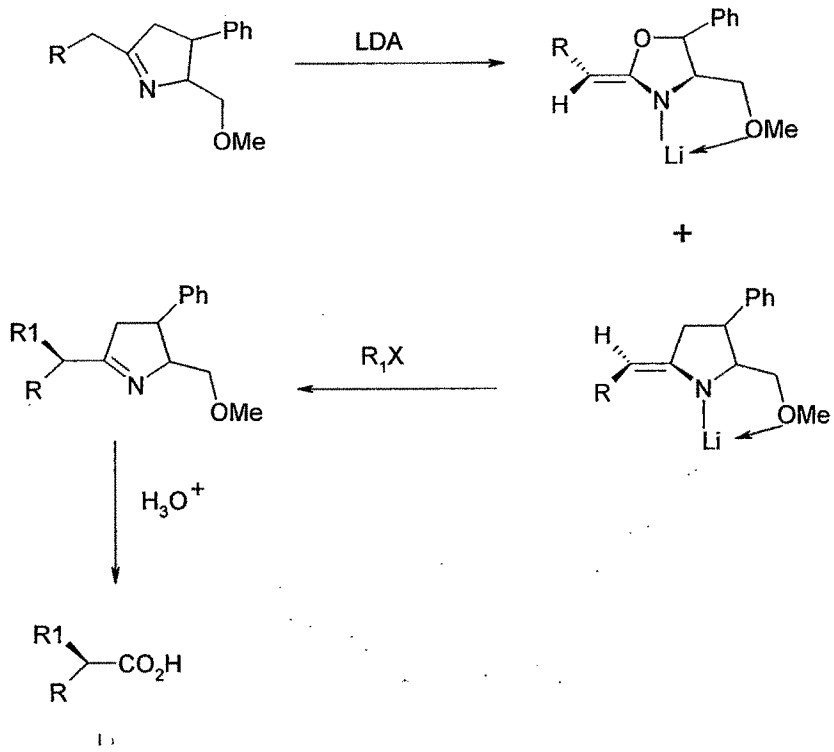
Oxazolines are useful intermediates for the asymmetric synthesis. Metallation of 69 with LDA followed by reaction with isobutyraldehyde and subsequent hydrolysis results in the formation of enantiomerically pure acids 70 **(Scheme I.21).**[54]



69 70

Scheme I.21

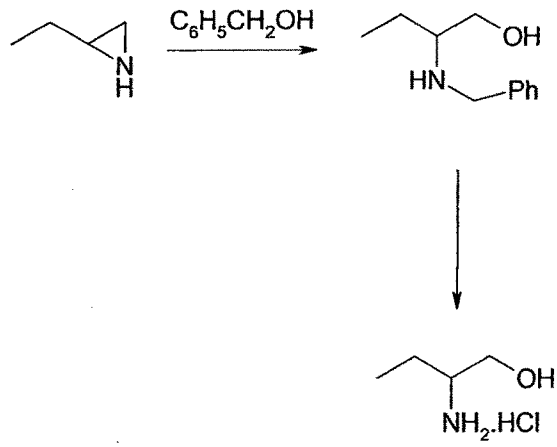
Metallation of the oxazoline provides an azaenolate 71 and 72. Reaction with the electrophile provides for a top face alkylation, subsequent hydrolysis results in the formation of optically pure acids 73 (**Scheme I.22**).[55]



Scheme I.22

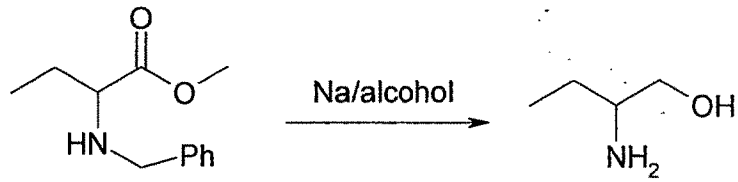
1.5 SYNTHESIS, & RESOLUTION OF 2-AMINO-1-BUTANOL

Treatment of 2-ethyl aziridine (74) with benzyl alcohol gave (+/-) N-benzyl- 2-amino-1-butanol (75) which on hydrolysis resulted in the formation of (+/-) 2-amino-1-butanolhydrochloride (76) (**Scheme 1.23**).[56]



Scheme I.23

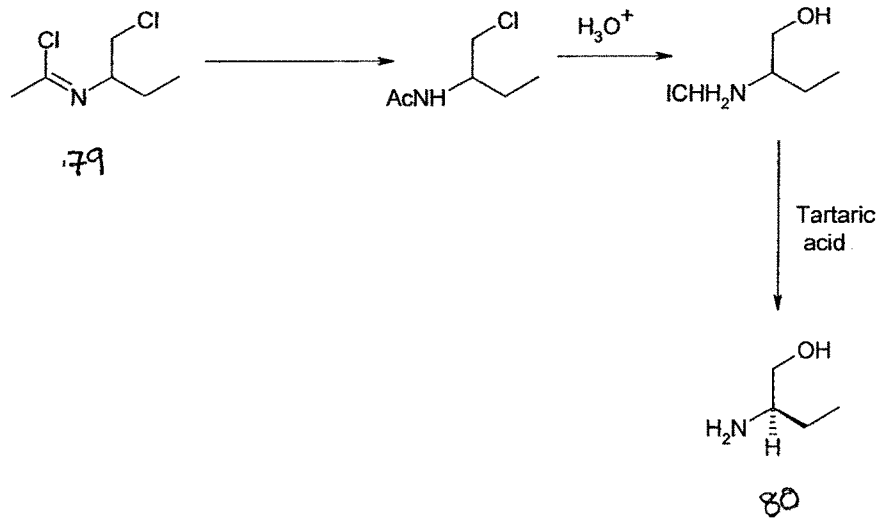
(+/-)-2-Amino-1-butanol(78) is synthesised by reduction of N-benzyl-2-aminomethyl butyrate(77) with sodium in alcohol (**Scheme I.24**).[57]



77 78

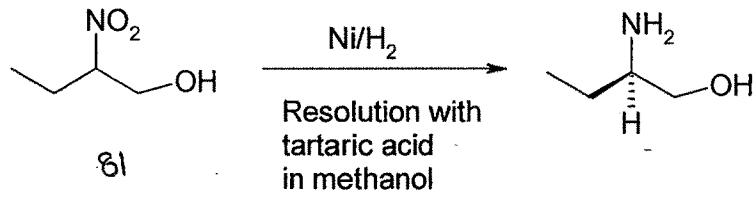
Scheme I.24

2-Amino-1-butanol was prepared by hydrolyzing N-(1-Chloromethylpropy)acetimidoyl chloride(79) to 1-Chloromethyl propylamine and hydrolyzing the latter to (+/-)-2-amino-1-butanolhydrochloride, which was resolved with L-tartaric acid to give R-(-)-2-amino-1-butanol(80)(**Scheme I.25**).[58]



Scheme I.25

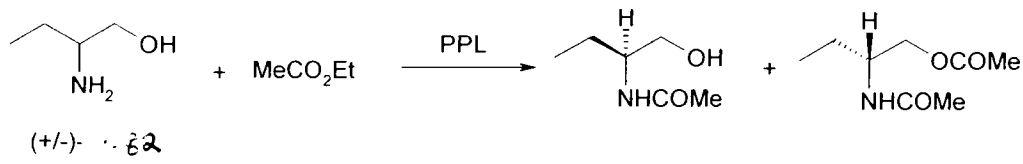
(*R*)-(-)-2-amino-1-butanol was also prepared in 31% overall yield by condensing nitropropane with formaldehyde and triethylamine to give 3-Nitropropanol(81), and reduction over Raney Ni and H_2 followed by resolution with tartaric acid in anhydrous methanol (**Scheme I.26**).[59]



Scheme I.26

(+/-)-2-Amino-1-butanol was heated with L-(+)-tartaric acid at 40-60°C, the mixture when cooled to 0°C resulted in precipitation of (-)-2-Amino-1-butyl L-(+)-tartrate and (+)-2-Amino-1-butyl L-(+)-tartrate.[60]

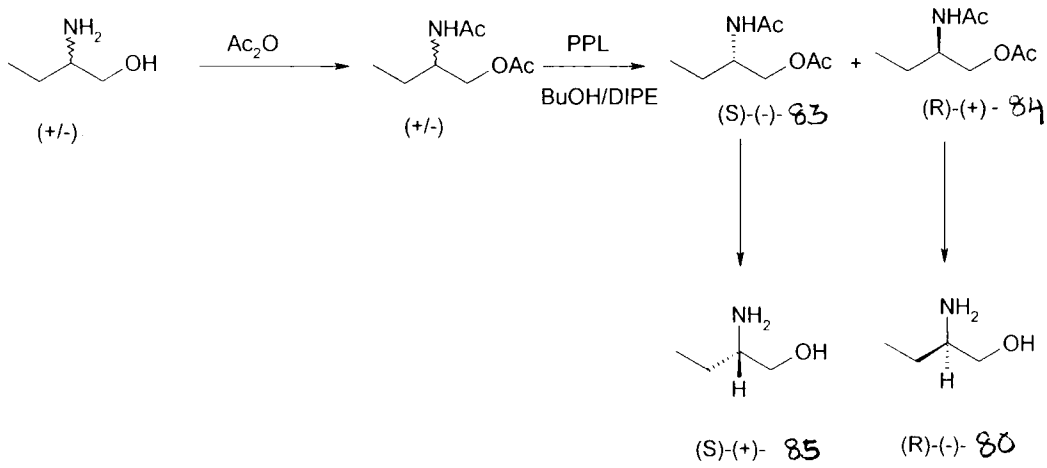
Procine pancreatic lipase catalysed the enantioselective N- and O-acylation of 2-aminobutan-1-ol(82) (**Scheme I.27**).[61]



(+/-)- 82

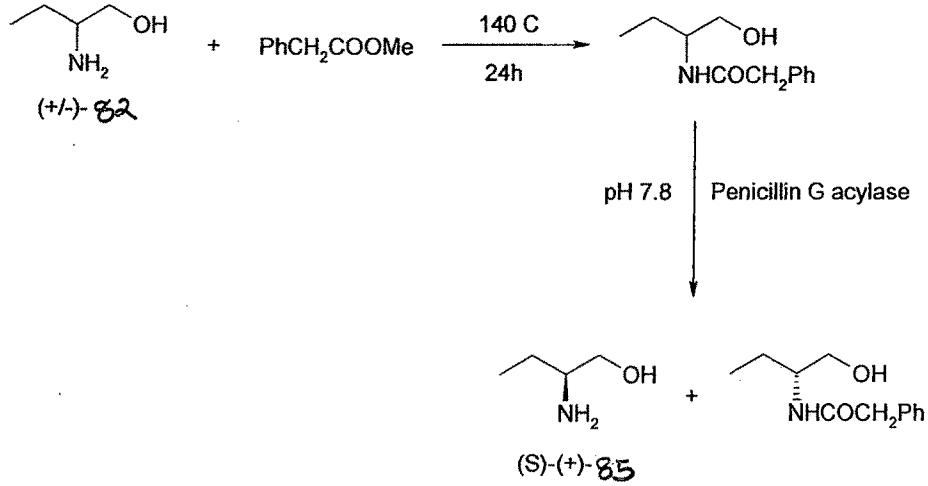
Scheme I.27

Acetylation of (+/-)-2-Amino-1-butanol gave diacetyl derivative of 2-Amino -1-butanol which upon lipase-catalyzed transesterification with n-butanol gave the diacetyl derivatives (*S*)-(-)-83 and (*R*)-(+)-84. The hydrolysis of 83 gave (*S*)-(-)-2-Amino-1-butanol which is a synthetic precursor for ethambutol and the hydrolysis of 84 gave (*R*)-(+)-2-Amino-1-butanol(80) (**Scheme I.28**).[62]



Scheme I.28

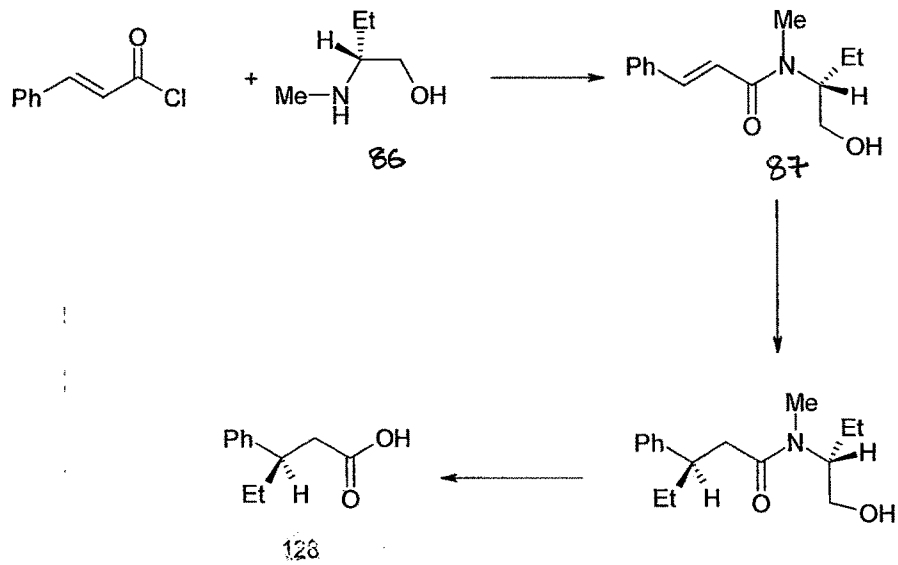
Racemic 2-Amino-1-butanol(82) has been resolved to obtain (S)-2-amino-1-butanol(85) with via enantioselective hydrolysis of its N-phenylacetyl derivative with penicillin G acylase immobilised on Eupergit (**Scheme I.29**).[63]



Scheme I.29

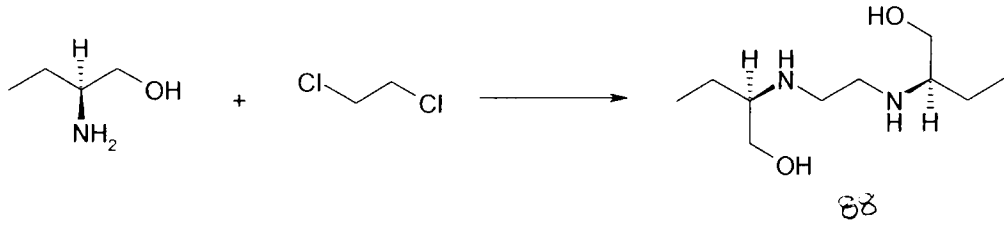
1.6 REACTIONS OF 2-AMINO-1-BUTANOL

Reaction of cinnamoyl chloride with N-methyl-2-amino-1-butanol (86) afforded the corresponding cinnamamides (87). Michael additions of Grignard reagents to the latter followed by acidic hydrolysis, yielded optically active β-phenyl-β-ethyl propanoic acid (**Scheme I.30**).[64]



Scheme I.30

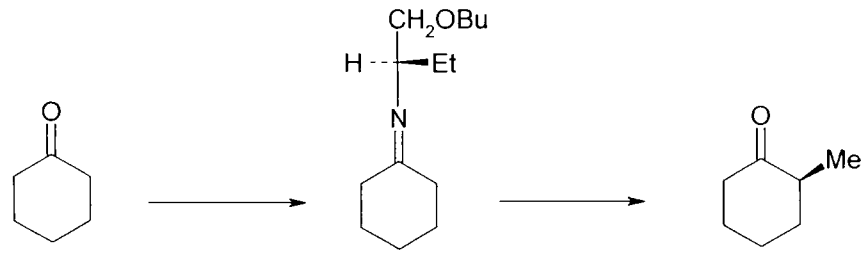
Condensation of (*S*)-(+)-2-Amino-1-butanol with dichloroethane at 80°C resulted in the formation of (+)-N,N'-Bis[1-(hydroxymethyl)propyl]ethylenediamine(88) is useful as a tuberculostatic agent (**Scheme I.31**).[65]



88

Scheme I.31

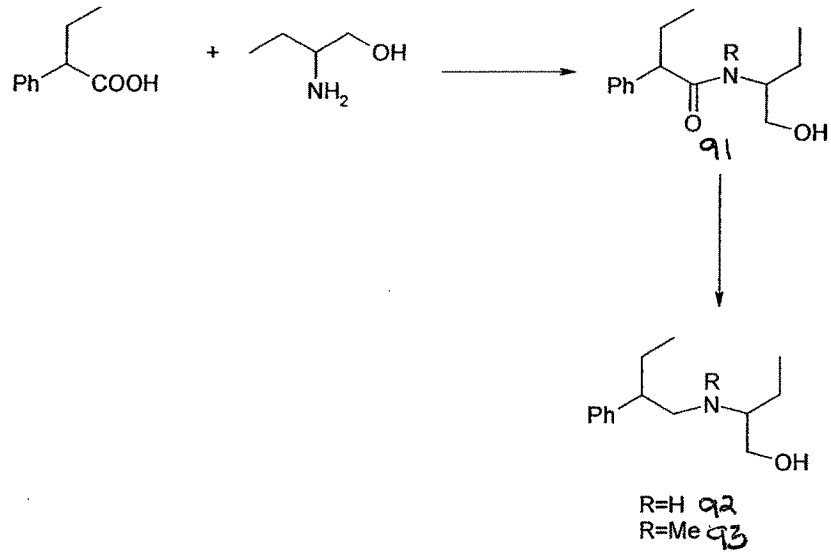
The imine 89 [from cyclohexanone and (*R*)-2-aminobutyl butyl ether] was converted to the anion which underwent alkylation at -78°C to give, after hydrolysis, (R)-2-methylcyclohexanone(90) with an optical purity of 81% (**Scheme I.32**).[66]



89 90

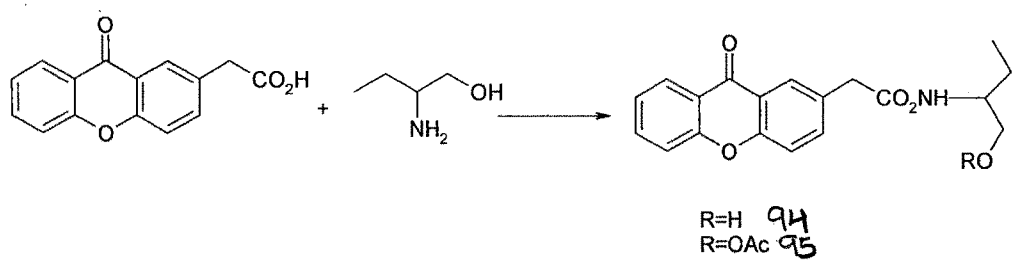
Scheme I.32

The optical isomers of amides(91) were prepared from 2-phenylbutyric acids and 2-aminobutanols, subsequent hydride reduction of which produced amines 92 which was methylated to 93 with formaldehyde and formic acid (**Scheme I.33**).[67]



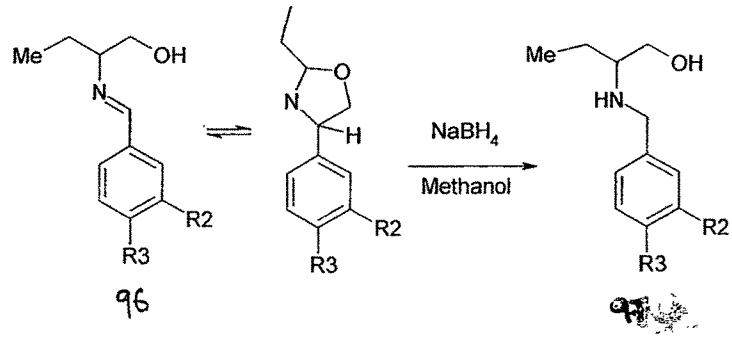
Scheme I.33

Racemic *N*-[2-(1-hydroxybutyl)]xanthone-2-acetamide (94) was prepared by refluxing xanthone-2-acetic acid and 2-Amino-1-butanol in xylene. Acetylation of 94 with Ac_2O gave its acetyl derivative 95 (**Scheme I.34**).[68]



Scheme I.34

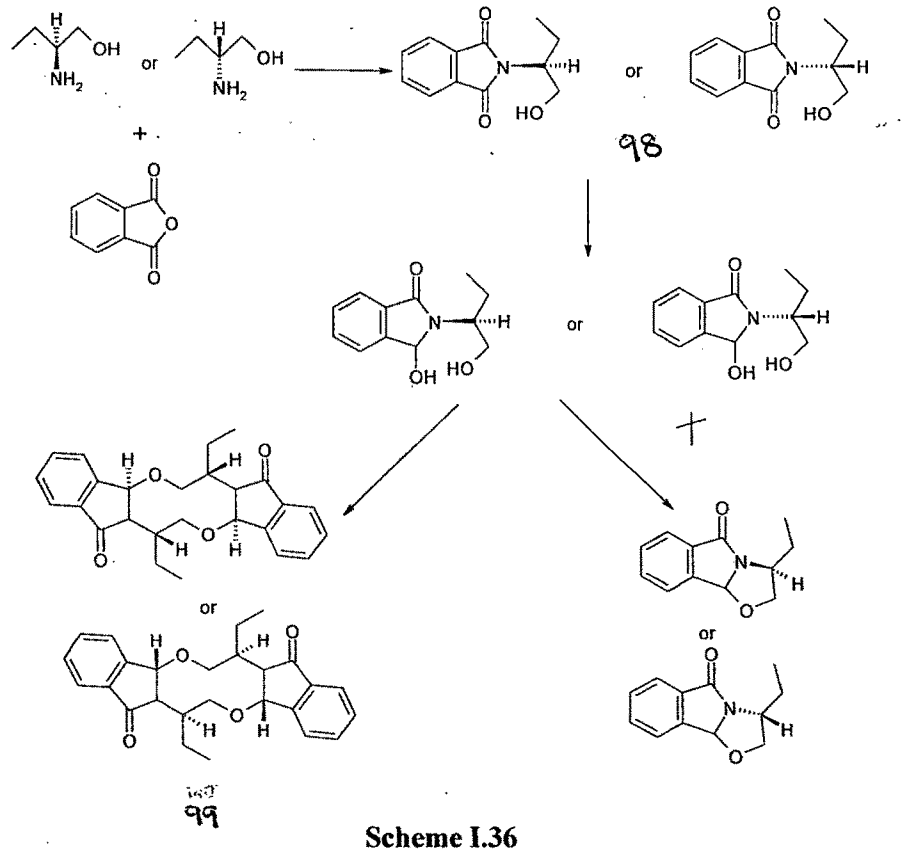
Chiral imines 96 , were derived from *(R)* and *(S)*-2-amino-1-butanol and the corresponding benzaldehydes. Some of the chiral imines have been found to be in equilibrium with the corresponding 1,3-oxazolidines, which on treatment with sodium borohydride in methanol are reduced to the corresponding N-benzyl derivatives 97 (**Scheme I.35**).[69]



R2 = H, NO , OMe ; R3 = H, Cl, Me, OMe

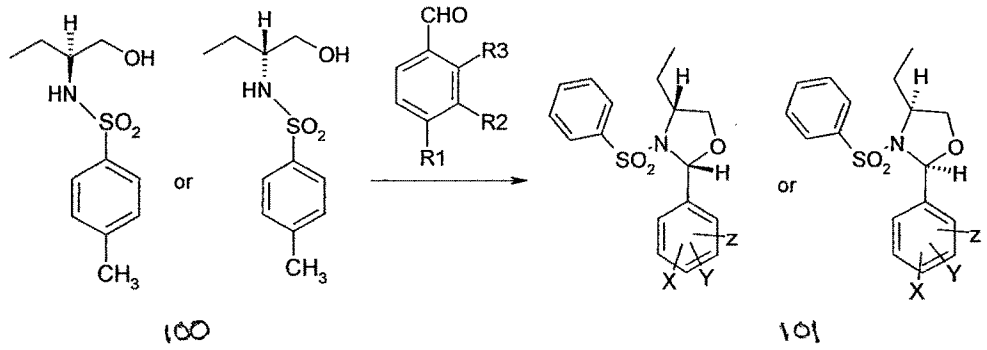
Scheme I.35

A novel chiral ten membered 99 [70] heterocyclic ring was synthesized in two steps from phthalamide derivatives 98 of (*R*) & (*S*)-2-Amino-1-butanol. The structures were unambiguously established by single crystal x-ray diffraction of one of the compounds **(Scheme I.36)**.



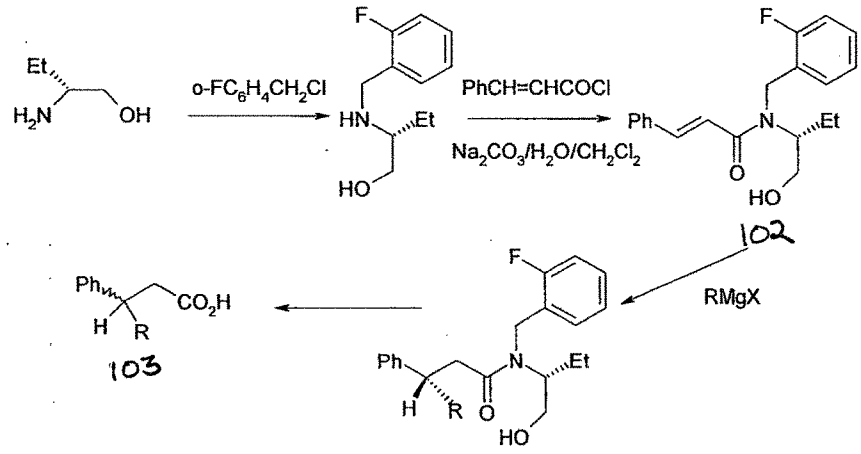
Scheme I.36

N-Arylsulfonamides(100) of (*R*) & (*S*)-2-Amino-1-butanols, on condensation with aromatic aldehydes produced diastereomerically pure 2-aryl-3-arenesulfonyl-4-ethyl-1,3-oxazolidines(101).[71] The absolute configurations of one enantiomeric pair have been detected from two fully refined X-ray structures, supplemented by NMR data (**Scheme I.37**).



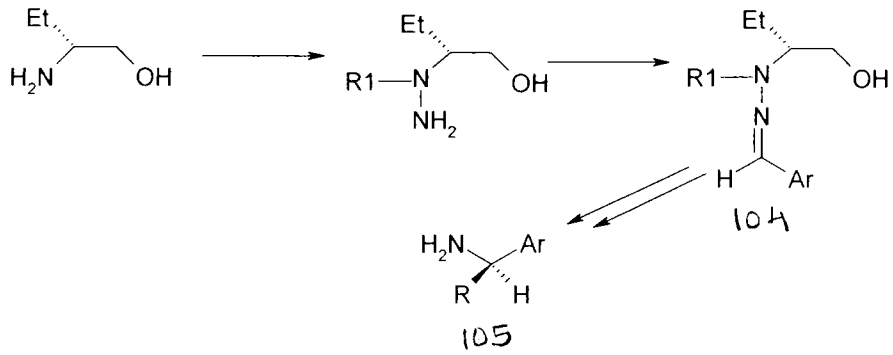
Scheme I.37

Conjugate addition of various Grignard reagents to the N-(2-fluorobenzyl)cinnamamide(102) afforded the corresponding adducts in good yields and in high diastereomeric excesses,acidic hydrolysis of these adducts gave the corresponding β-substituted alkanoic acids 103(**Scheme I.38**).[72]



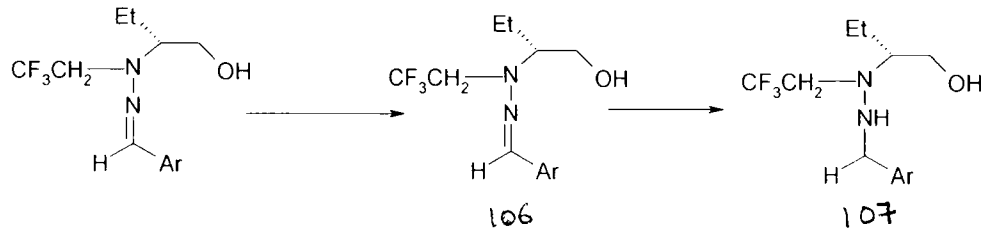
Scheme I.38

Reaction of various aromatic aldehydes with chiral hydrazine[73] derived from 2-aminobutan-1-ol gave the corresponding hydrazones 104. Enantioselective addition of EtMgBr or n-BuMgBr the trisubstituted hydrazines and further catalytic hydrogenolysis using Pd-C/H_2 afforded the enantiomerically enriched α-arylalkannamines 105 (**Scheme I.39**)



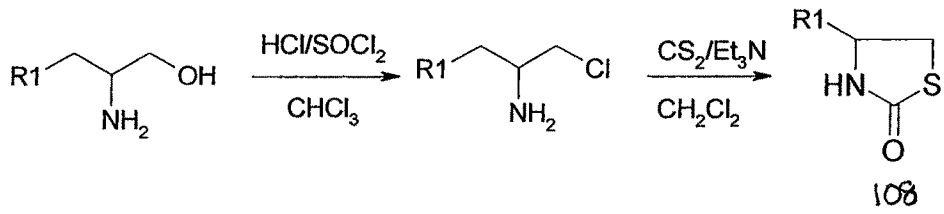
Scheme I.39

Various chiral N,N-dialkylhydrazines prepared from (R)-2-amino-1-butanol reacted with various prochiral ketones, thus giving the corresponding hyrazones 106, reduction of the latter by means of $LiAlH_4$ afforded N,N,N'-trisusbstitued hydrazines 107 whose des were in the range of 43-90% (**Scheme I.40**).[74]



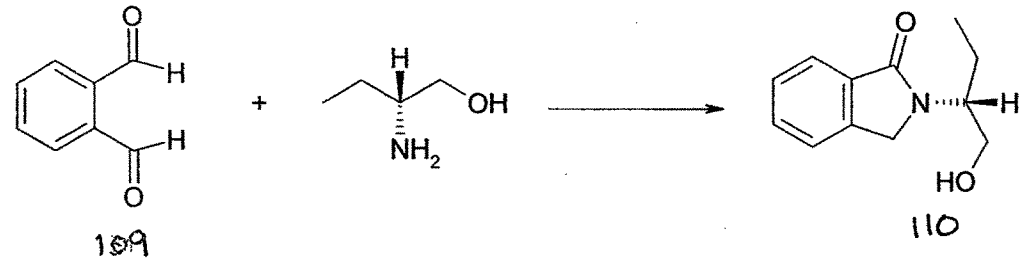
Scheme I.40

(*R*)-(-)-3-Benzoyl-4-ethylthiazolidine-2-thione (108). (R1 = -Et) is obtained in good yields from (*R*)-(-)-2-Amino-1-butanol (**Scheme 1.41**).[75]



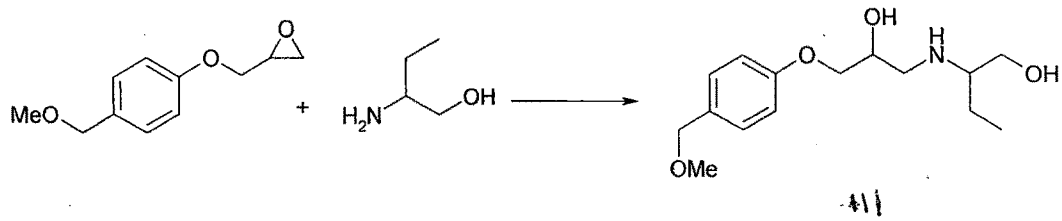
Scheme I.41

The reaction of o-phthalaldehyde (109) with (*R*)-(-)-2-aminobutanol yielded an unexpected rearrangement product, an N-substituted isoindoline-1-one (110) (**Scheme I.42**).[77]



Scheme I.42

4 diastereoisomers of metoprolol (111)[78] were synthesised by the reaction of racemic 2-[4-(2'-methoxyethyl)-phenoxymethyl]-oxirane with (*R*) & (*S*)-2-Amino-1-butanol. These novel derivatives present significant hypotensive and bradycardiac activity, although no blocking action toward β_1 and β_2 adrenergic receptor was observed (**Scheme I.43**).



Scheme I.43

1.7 REFERENCES

1. '*The alkanol amines Hand Book*', The Dow Chemical Co. **1981**.
2. Pasto, M.; Castejon, P.; Moyano, A.; Pericas, M.A.; Riera, A. *J.Org.Chem.* **1996**, *61*, 6033.
3. Bunnage, M.E.; Davies, S.G.; Goodwin, C.J. *J.Chem.Soc., Perkin Trans.1* **1994**, 2385.
4. Li, G.; Chang, H,-T.; Sharpless, K.B. *Angew.Chem., Int.Ed.Engl.* **1996**, *35*, 451.
5. Delair, P.; Einhorn, C.; Einhorn, J.; Luche, J. L. *J.Org.Chem.* **1994**, *59*, 4680.
6. Fehrentz, J.-A.; Califano, J.-C.; Amblard, M.; Loffet, A.; Martinez, J. *Tetrahedron Lett.* **1994**, *35*, 569.
7. Polt, R.; Peterson, M.A. *Tetrahedron Lett.* **1990**, *31*, 4985.
8. Beaulieu, P.L.; Wernic, D.; Duceppe, J.S.; Guindon, Y. *Tetrahedron Lett.* **1995**, *36*, 3317.
9. Takahashi, H.; Sakuraba, S.; Takeda, H.; Achiwa, K. *J.Am.Chem.Soc.* **1990**, *112*, 5876.
10. Hartung W.H. *Chem.Rev.* **1931**, *9*, 389.
11. Umezawa, H; Aoyagi, T; Suda, H; Hamada, M.; Takeuchi, T. *J.Antibiot.* **1976**, *29*, 97.
12. Nakamura, H.; Suda, H.; Takita, T.; Auyagi, T.; Umezawa, H. *J.Antibiot.***1976**, *29*, 102.
13. Ino, K.; Goto, S; Nomura, S.; Isobe, K.I.; Nawa, A; Okamoto, T; Tomoda, Y. *Anticancer Res.* **1995**, *15*, 2081.
14. Haddad, M; Botuha, C.; Larcheveque, M. *Synlett* **1999**, 1118.
15. O'Connell, C.E.; Salvato, K.A.; Meng, Z.; Littlefield, B.A.; Schwartz, C.E. *Bioorg.Med.Chem.Lett.* **1999**, *9*,1541.
16. Wagner, B.; Gonzalez, G.I.; Dau, M.E.T.H; Zhu, J. *Biorg.Med.Chem.* **1999**, *7*, 737.
17. Dinh, T.Q.; Du, X.; Smith, C.D.; Amstrong, R.W. *J.Org.Chem.* **1997**, *62*, 6773.
18. Shimojima, Y; Shirai, T.; Baba, T.; Hayashi, H. *J.Med.Chem.* **1985**, *28*, 3.

19. Shimojima, Y.; Hayashi, H; Ooka, T.; Shibukawa, M.; Iitoka, Y. *Tetrahedron* **1984**, *40*, 2519.
20. Hannun, Y.A.; Linardic, C.M. *Biochem.Biophys.Acta.* **1993**, *1154*, 223.
21. Kamiyama, T.; Umino, T.; Itezuno, Y.; Nakamura, Y.; Satoh, I. *J. Anitibiot.* **1995**, *48*, 929.
22. Bagii, J.F.; Kluepfel, D.; St. Jacques, M. *J.Org.Chem.* **1973**, *38*, 1253.
23. Kobayashi, J.; Cheng, J.,-F.; Ishibashi, M.; Walchii, M.R.; Yamamura, S. *J.Chem.Soc., Perkin Trans. 1* **1991**, 1135.
24. Schaefer, J.P.; Wheatley, P.J. *J.Org.Chem.* **1968**, *33*, 166.
25. He, A.-W.R.; Cory, J.G. *Anticancer Res.* **1999**, *19*, 421.
26. Koepili, J.B.; Brockman Jr., J.A.; Moffat, J. *J.Am.Chem.Soc.* **1950**, *72*, 3323.
27. Elbein, A.D. *FASEB J.* **1991**, *5*, 3055.
28. Lown, W. In '*Anthracycline and Anthracendione-Based Anti Cancer Agents*', Elsevier: Amsterdam, **1988**.
29. Sugwara, H.; Tsunakawa, M.; Konishi, M.; Kawaguchi, H.; Krishnan, B.; Cun-heng, H.; Clardy, I. *J.Org.Chem.* **1987**, *52*, 996.
30. Kakeya, H.; Morishita, M; Koshino, H; Morita, T; Kobayashi,K; Osada, H. *J.Org.Chem.* **1999**, *64*, 1052.
31. Kulanthaivel, P.; Hallock,Y.F.; Boros, C.; Hamilton, S.M.; Janzen, W.P.; Ballas, L.M.; Loomis, C.R.; Jiang, J.B.; Katz, B.; Steiner, J.R.; Clardy, J. *J.Am.Chem.Soc.* **1993**, *115*, 6452.
32. Hu, H.; Hollinshead, S.P.; Hall, S.E.; Kalter, K.; Ballas, L.M. *Bioorg.Med.Chem.Lett.* **1996**, *6*, 973.
33. Crane, H.M.; Menaldino, D.S.; Jagdmann Jr., G.E.; Darges, J.W.; Buben, J.A. *Bioorg.Med.Chem.Lett.* **1995**, *5*, 2133.
34. Rodriguez, A.D.; Soto, J.J. *Tetrahedron Lett.* **1996**, *37*, 2687.
35. Ohta, Y.; Shinkai, I. *Bioorg. Med.Chem.* **1997**, *5*, 465.
36. Tok, J.B.H.; Rando, R.R. *J.Am.Chem.Soc.*, **1998**, *120*, 8279.
37. Hallinan, E.A.; Tsymbalov, S.; Finnegan, T.M.; Moor, W.M.; Jerome, G.M.; Currie, M.G.; Pitzele, B.S. *J.Med.Chem.* **1998**, *41*, 775.
38. Whitesell, J.K.; Whitesell, M.A. *J.Org.Chem.* **1977**, *42*, 377.

39. Meyers, A.I.; Williams, D.R.; Druelinger, M. *J.Am.Chem.Soc.* **1976**, *98*, 3032.
40. Myers, A.G.; Yang, B.H.; Chun, H.; Gleason, J.L. *J.Am.Chem.Soc.* **1994**, *116*, 9361.
41. Suzuki, Y.; Takahashi, H. *Chem.Pharm.Bull.* **1982**, *30*, 3160.
42. Takahashi, H; Inagaki, H. *Chem.Pharm.Bull.* **1982**, *30*, 922.
43. Wu, M, -J.; Pridgen, L.N. *Synlett* **1990**, 636.
44. Wu, M, -J.; Pridgen, L. N. *J.Org.Chem.* **1991**, *56*, 1340.
45. Neelakantan, L. *J.Org.Chem* **1971**, *36*, 2256.
46. Takahashi, T.; Suzuki, Y.; Kamatani, T. *Heterocycles* **1983**, *20*, 607.
47. Cardani, S.; Poli, G.; Scolastico, C.; Villa, R. *Tetrahedron* **1988**, *44*, 5929.
48. Kolb, M.; Barth, J. *Tetrahedron Lett.* **1979**, 2999.
49. Evans, D.A.; Takacs, J.M.; Mc Gee, L.R.; Ennis, M.D.; Math, D.J.; Bartoli, J. *Pure Appl.Chem.* **1981**, *53*, 1109.
50. Enders, D.; Eichenauer, H. *Tetrahedron Lett.* **1977**, 191.
51. Evans, D.A.; Ennis, M.D.; Mathre, D. J. J.Am.Chem.Soc. **1982**, *104*, 1737.
52. Evans, D.A.; Urpi, F.; Somers, T.C.; Clark, J.S.; Bilodeau, M.T. *J.Am.Chem.Soc.* **1990**, *112*, 8215.
53. Evans, D.A.; Sjogron, E.B. *Tetrahedron Lett.* **1985**, *26*, 3783.
54. Meyers, A.I.; Whitten, C.E. *J.Am.Chem.Soc.* **1975**, *97*, 6266.
55. Meyers, A.I.; Knaus, G. *J.Am.Chem.Soc.* **1974**, *96*, 6508.
56. Belzecki, C.; Tomasik, W.; Trojnas, J. *Pol. Pat.*, 86457, **1977**; CA **1979**, *90*, 43293z.
57. Nargund, P.K.; Mehra, R.K.; Fulwadiwala, P.B.S.; Mehta, S.C.R. *Indian Pat.*, 139,104, **1976**; CA **1980**, *92*, 163566c.
58. Singh, B. *S.African Pat.* ZA 7600577, **1976**; CA **1976**, *84*, 183977.
59. Hu, Z.S.; Mei, W.C.; Heng, Y.C. K'o Hsuch Fa Chan Yuch K'an **1982**, *10*, 602; CA **1983**, *98*, 71438h.
60. Sturzu, L.; Kevorkian, M. *Rom.Pat.* RO 72333, **1980**; CA **1980**, *92*, 217229.
61. Gòtor, V.; Brieva, R.; Rebolledo, F. *J.Chem.Soc., Chem.Commun.* **1988**, 957.
62. Bevinakatti, H.S.; Newadkar, R.V.; Ravindra, V. *Tetrahedron: Asymm.* **1990**, *1*, 583.

63. Fadnavis, N.W.; Sharfuddin, M.; Vadivel, S.K. *Tetrahedron: Assym.* **1999**, *10*, 4495.

64. Bataille, P.; Paterne, M.; Brown, E. *Tetrahedron: Asymm.* **1999**, *10*, 1579.

65. Adrian, G.; Sion, M.X. *Fr. Demande FR. Pat.* 2351090, **1977**; CA **1976**, *84*, 146407.

66. Whitesell, J.K.; Whitesell, M.A. *J.Org.Chem.* **1977**, *42*, 377.

67. Eckstein, M.; Celga, M.; Gajewczyk, L. *Arch.Pharm.* **1986**, *319*, 630.

68. Marona, H. *Acta Pol.Pharm.* **1990**, *47*, 65.

69. Kumar, G.B.; Shah, A.C. *Indian J.Chem., Sect. B.* **1996**, *35B*, 79.

70. Kumar, G.B.; Shah, A.C.; Pilati, T. *Tetrahedron Lett.* **1997**, *38*, 3297

71. Kumar, G.B.; Patel, H.; Shah, A.C.; Trenkle, M.; Cardin, C.J. *Tetrahedron: Asymm.* **1996**, *7*, 3391.

72. Brown, E.; Deroye, C.; Touet, J. *Tetrahedron: Asymm.* **1998**, *9*, 1605.

73. Bataille, P.; Paterne, M.; Brown, E. *Tetrahedron: Asymm.* **1998**, *9*, 2181

74. Bataille, P.; Paterne, M; Brown, E. *Tetrahedron: Asymm.* **2000**, *11*, 1165.

75. Yadav, L.D.S.; Dubey, S. *Indian J.Chem.*, Sect. B. **2002**, *41B*, 593.

76. Kumar, G.B.; Shah, A.C.; Cardin, C.J.; Trenkle, M. *Acta Crystallographica*, **1999**, *C55*.

77. Melgar-Fernandez, R.; Demare, p.; Hong, E.; Rosas, M.A.; Escalante, J.; Munoz-Muniz, O.; Juaristi, E.; Relga, I. *Bioorganic & Med. Chem. Lett.* **2004**, *14*, 191.