NEW ADVANCED SYNTHETIC APPROACH ON PHARMACOPHORE 1,2-AMINO ALCOHOLS

B.Sreekanth[*], Dr C.M.Bhaskar Reddy,[**] Dr S.G. Manjunatha[***]

[*] Research Scholar,Dept of Chemistry,Rayalaseema University, Kurnool,Ap,India

[**] Research Scholar,Dept of Chemistry,Rayalaseema University, Kurnool,Ap,India

*** Research Guide, Rayalaseema University, Kurnool, Ap,India

DOI: 10.29322/IJSRP.8.6.2018.p7829
http://dx.doi.org/10.29322/IJSRP.8.6.2018.p7829

Abstract- The main aim and objective of this research paper is to prepare pharmacophore 1, 2- amino alcohols. Amino alcohols are prepared by ring opening with nitrogen nuclophiles from Cyclicsulfates which was consequentialised via asymmetric dihydroxylation of the corresponding alkenes. 1,2-amino alcohols prepared by ring opened with nitrogen nuclophiles from carbonates which was derived via asymmetric dihydroxylation of the corresponding alkenes. The opening occurs in the generally activated position with overall yields of 70-80% . Similarly, synthesised syn-amino alcohols from syn-diols. These compounds are more useful to cure infections obtained from Gram positive and Gram negative Bacteria in human beings.

Index Terms- Pharmacophore, 1,2-Amino alcohols, Diastereoselectivity, antimicrobial and antibiotics

INTRODUCTION

In synthetic organic chemistry amino acids have not only been used as chiral building blocks ,they also used as chiral auxillaries an excellent source of stereo centre. In this paper we designed simple methods to prepare pharmacophore 1, 2-amino alcohols. It gives a brief introduction to amino alcohol and naturally occurring amino molecules. It will give the flavour of synthetic pharmacological active molecules, ligands and chiral auxiliaries. It is included the preparation of 1, 2-amino alcohols from different functional groups.

Amino alcohols contain both an amine and an alcohol functional group. These amino alcohol containing compounds range from important physiological constituents of human body, like the hormone epinephrine and amino acid serine, natural products, to peculiar secondary metabolite, like ammonal and calyculin encountered in deep sea creatures. Subsequently these molecules show interesting biologically active responses, such as antimicrobial, antibiotics, antifungal activities, tuberculosis, alkaloids, enzyme inhibitors, β-blockers glycosphingolipids and amino sugars. So these are playing very important role in medicinal, pharmaceutical and organic chemistry. General formula for amino alcohol is R-CH (OH)-CH_2-NH_2. Here R is alkyl or aryl chain. Depending on position of OH, NH_2 groups molecules are classified as 1, 2-Amino alcohol, 1, 3-Amino alcohol.

1.1 Introduction of 1, 2-Amino alcohol

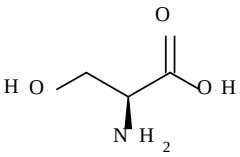
1, 2-amino alcohols moiety is a widespread structural part in a huge collection of naturally taking place and artificial molecules. Alternative names are vicinal amino alcohol, β-amino alcohol. These are 3 types in literature.

1. Naturally occurring molecules
2. Synthetic pharmacologically active molecules

3. Chiral catalysts and auxiliaries

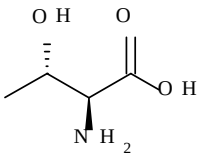
1.1.1 Naturally occurring molecules

Naturally occurring hydroxy amino acids have an amino alcohol group. Examples, Serine (1) and threonine (2) are both biologically important, useful for chiral pool[1]. Similar well-known examples are shown in below Figure-1. This group is a part of bestatin[2] synthesis. Bestatin (3) contains a syn-α -hydroxy-β-amino acid, act as amino peptidase inhibitor exhibits, shows immune modulatory action [3,4] and also is used for cancer chemotherapy.[5] Second example is the lactone AI-77-B (4)[6-10] , which is naturally isolated from the culture broth of bacillus pumilus. It is synthesized from lactone and diacid side chain in laboratory, structurally unique molecule and shows gastro protective activity. Many synthetic methods have been reported[11-13] in literature.



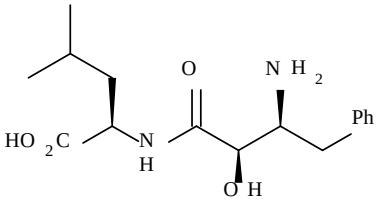
1

L- Serine



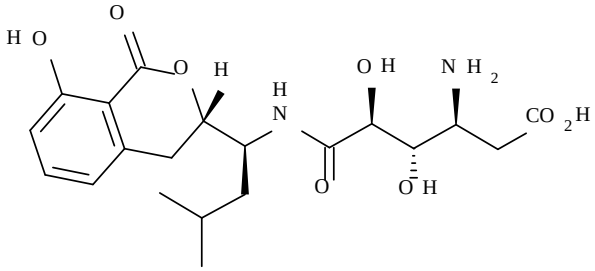
2

L- threonine



3

Bestatin

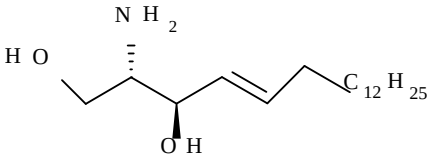


4

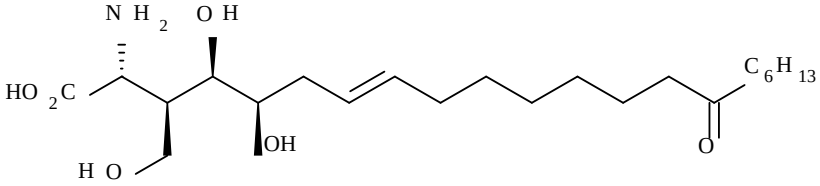
Al-77-B

Fig-1: Hydroxy amino acids

Naturally occurring a large number of lipids and similar molecules contains 1,2-amino alcohol moiety (Fig.2). One of the example, sphingosine (5)[14], it is a bio molecule and important in cell signaling.[15] Myriocin (6) is one of the example for structurally similar to lipids.[16,17] It contains more than one acid group and amino alcohol group, which are isolated from the thermophilic ascomycete M. Albomyces. It is act as potent immunostimulatory agents.



5

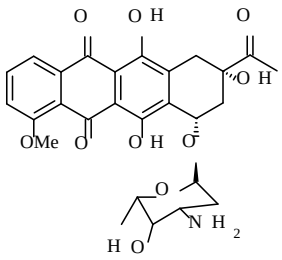


6

Fig 2: Lipids

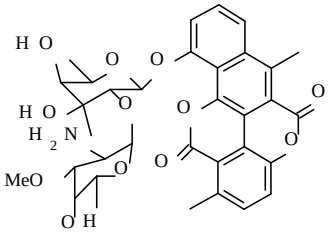
Sugars (Fig. 3) another class of molecules containing the 1, 2-amino alcohol, which **are components of larger molecules either aglycones or other sugars.** Daunomycinis (7) one member of a great category of glycosylated anthracycline natural products.[18] It **is prepared from aglycone daunomycinone is glycosylated with the sugar daunosamine .**

Sugar portion of glycosylated natural products is necessary for biological activity.One more example is ElsamicinA (8), which is one more replica of a polycyclic aromatic aglycon linked to an amino substituted sugar.[19-21] It will act as an antitumor antibiotic and presence of sugar group, improve the biological activity and water solubility of the antibiotic. Neomycin B (9) is one member of a big group of amino glycoside antibiotics. These used for the treatment of Gram negative and Gram-positive bacteria infections.[22]



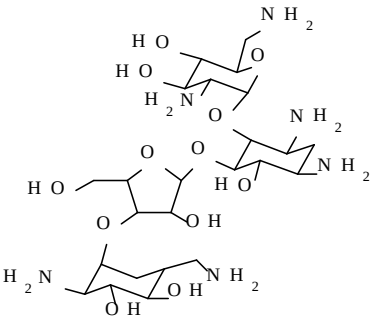
7

Daunomycin



8

Elsamicine A



9

Neomycine B

Fig 3: Sugars

Naturally isolated variety of amino alcohols contained molecules show a wide range of biological activities. So this created very much interest to pharmaceutical industries to synthesis of molecules.

1.1.2 Synthetic pharmacologically active molecules

The skeleton of the type 10 (Fige-4), is particularly interesting in biologically active pharmaceutical compounds, which are easily available via one-pot multi component reaction process. Compounds such as Propranolol (11) are used as selective dopamine D4 receptor antagonists.[23] Some amino alcohol derivatives 12 prove to be useful as antagonists of the calcium receptor I that inhibits parathyroid hormone secretagogues[24], other compounds such as Practolol (13), Celiprolol hydrochloride (14), Salbutamol (15) and Metoprolol (16) are the drugs belonging to the class of Arloxypropanolamine (10) useful as β-blocker.[25, 26]

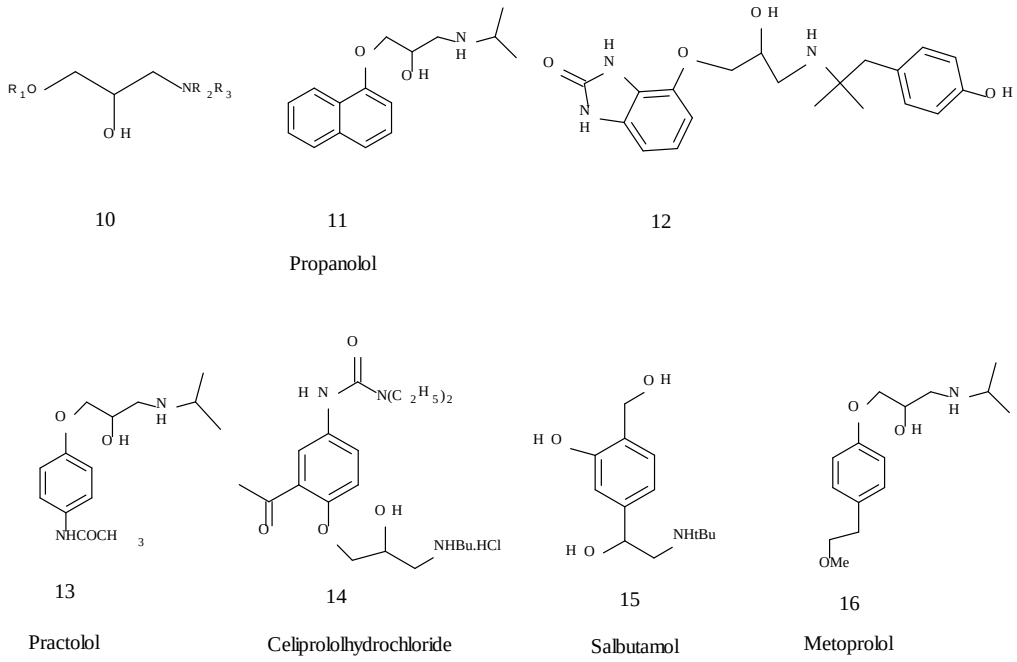
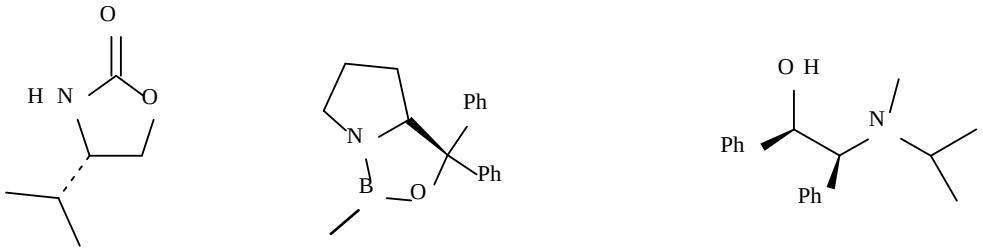


Fig 4: Pharmacologically active molecules

1.1.3 Ligands and chiral auxiliaries

Many enantiomerically pure amino alcohols used as Ligands or chiral auxiliaries (Fig. 5)[27,28] `Evans auxiliaries' (17) [29] is the good examples for it. These amino alcohols synthesized from oxazolidinones. Prepared oxaborolidines (18) from proline. It is specially used for the asymmetric reductions of carbonyl compounds.[30] The ephedrine derivative (19) used as a chiral proton, reduce to deracemizean enolate.[31] Largely amino alcohols used as ligands or chiral auxiliaries are extracted from natural sources

such as amino acids. These are generally customized to improve their chelating capability or improve their steric overcrowding effects.



17 18 19

Fig 5

I. EXPERIMENTAL

1.2 Previous artificial routes

In literature, there are large numbers of synthetic routes available for the synthesis of 1, 2-aminoalcohols. We cannot be present every method in this review, but we will present several examples based on generalised method to prepare the amino alcohols with the inherent limitation of accessible targets.

The disconnection approach of amino alcohols classified three types.

1. Coupling reactions
2. Amino hydroxylation
3. Addition of one heteroatom

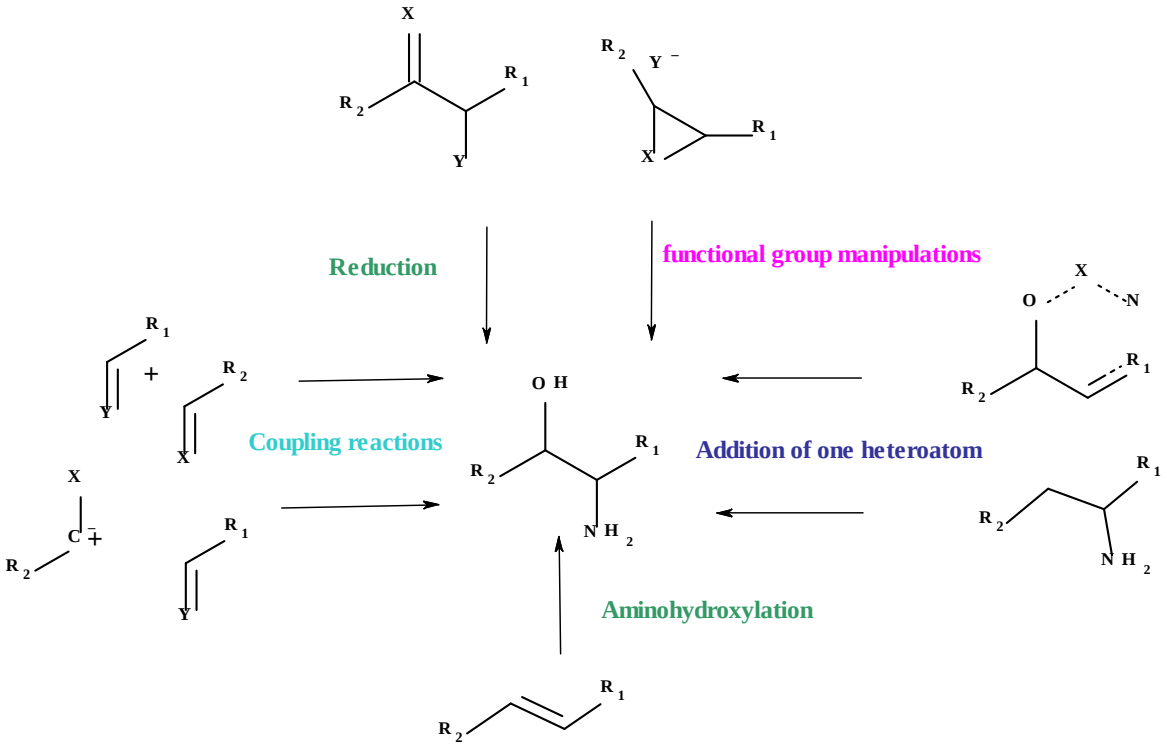
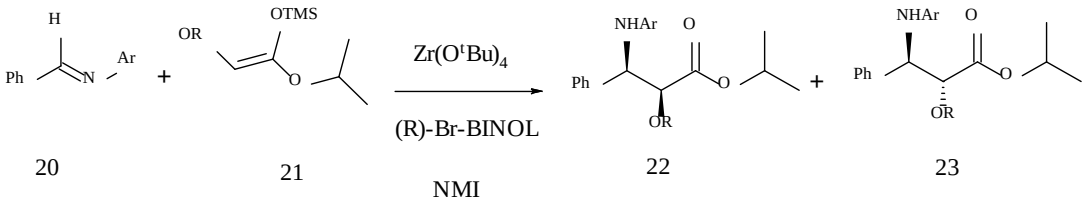


Fig 6: General disconnections for the synthesis of 1,2-amino alcohol

1.2.1. Coupling reactions

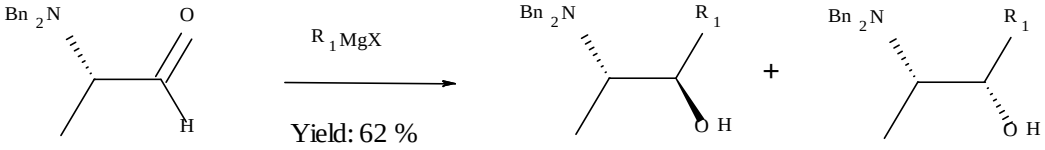
Mainly efficient synthesis of amino alcohols should be the combination of one molecule containing oxygen functionality and other nitrogen functionality of molecules. Newly two stereo centers are generated at the same time; both enantio and diastereoselectivity have to be restricted. The approach is normally restricted by the structural anxiety on the substrates, in position to get prominent selectivity. Amino alcohols with elevated enantioselectivity[32] obtained by neclophilic addition to imines. Syn /Anti (isomer) major isomer ((Scheme 1) [33] formation will be fix by enolate in the addition of α-alkoxyenolates to aldimines. Jorgensen explained a proline-catalyzed α-amination of ketones using an azodicarboxylate as the nitrogen supply in current testimony. α-hydrazino ketones obtained with good enantio selectivities, and can be further plagiaristic into syn- or anti-amino alcohols by chronological reduction steps.[34]



20 21 22 23

Scheme 1: Nuclophilic addition to an imine

Good diastereoselectivity of molecule generated by using chiral molecule in the addition of organ metallic nucleophiles to α-aminocarbonyls, resulting from chiral amino acids (Scheme 2).[35] The asymmetric orientation get in the reaction can be explained by means of the Felkin-Anh non-che molation control model. Disadvantage of this method is the stability evils of α-amino carbonyls and occasionally reasonable diastereoselectivity attained.[36]

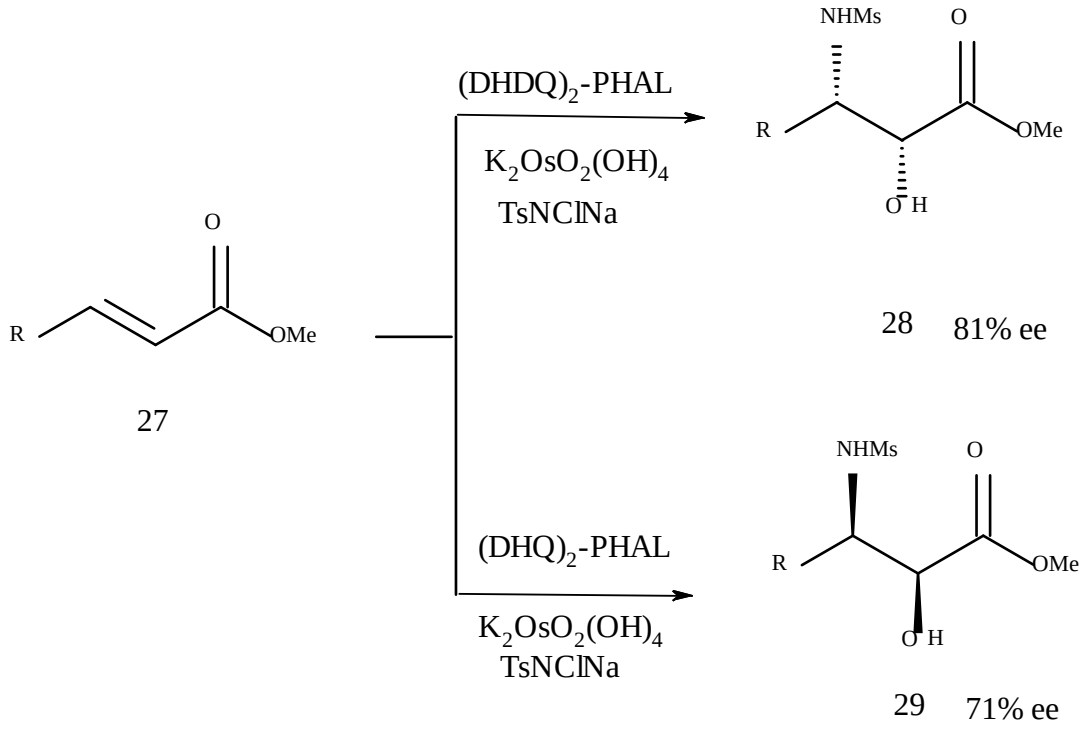


24 25 26

Scheme 2

1.2.2 Amino hydroxylation

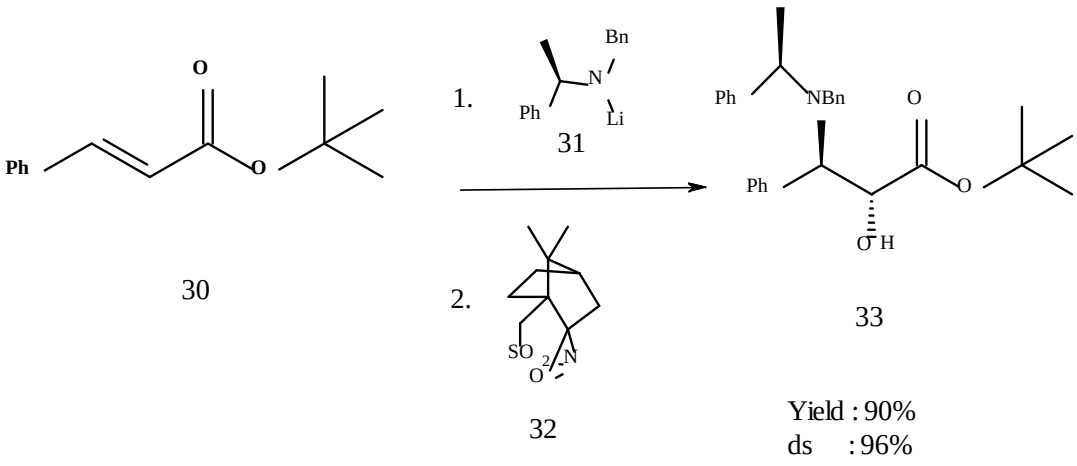
Sharpless has developed new osmium-catalyzed asymmetric amino hydroxylation process exemplified by the synthesis of the enantiomers of taxol side chain (28 and 29) from methylcinnamate (27) showed in the scheme-3. This method is direct approach for synthesis of asymmetric amino hydroxylation of alkenes, in which employed the similar oxidant and ligand method. α, β-Unsaturated esters and phosphonates are the most excellent substrates used for reaction, which convey syn-amino alcohols with high enantio selectivities but frequently with reasonable yields showed in below scheme [37].



Scheme 3: Sharpless asymmetrc aminohydroxylation

The extremely diastereoselective conjugate adding of lithium N-benzyl-N-α-methylbenzylamide with enoate acceptors, and the electrophilic hydroxylation of the resultant β-amino enolates with (camphorsulfonyl)oxaziridine, is identified as a direct and general strategy for the asym synthesis of homochiral β-amino-α-hydroxy acids and their derivatives described by Dave.[38]

In this reaction order, a chiral amide anion reacted to an α, β-unsaturated ester. The ensuing enolate ensnared with an oxygen electrophile to yield the anti-amino alcohol with outstanding diastereoselectivity (Scheme 4).

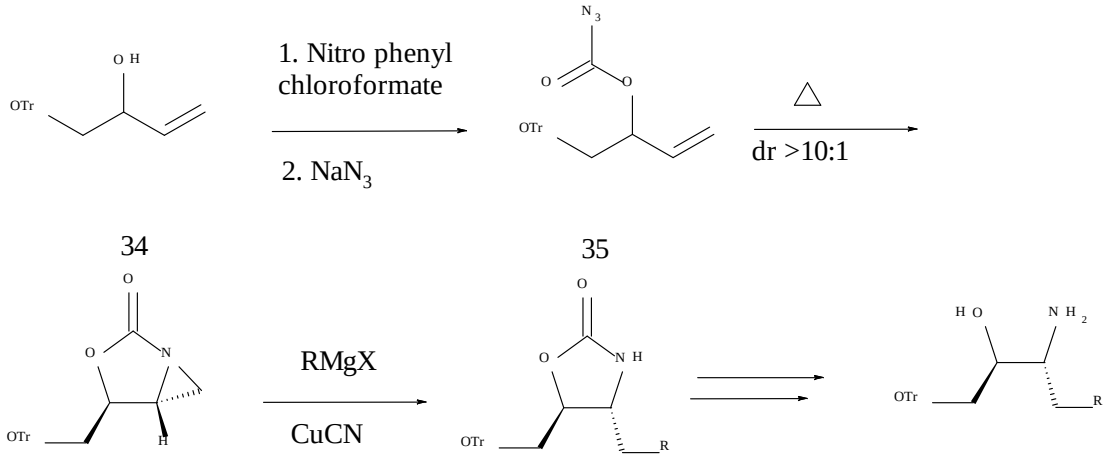


Scheme 4: Aminohydroxylation

The above mentioned methods have limited substrate and functional group forbearance, which can be typified by the amino hydroxylation of cyclohexane. The matching syn amino alcohol was got with fewer yields with poor enantioselectivity.

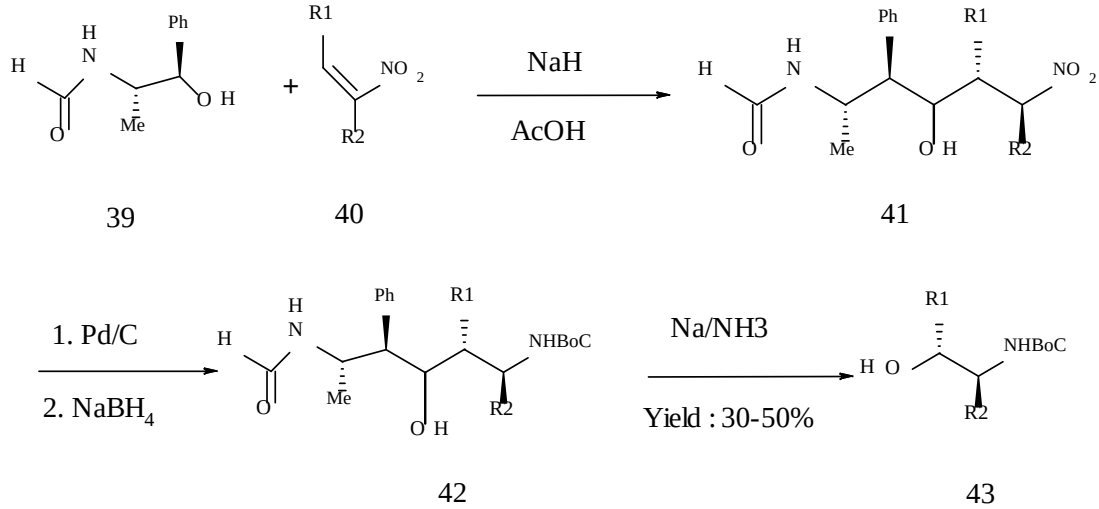
1.2.3 Addition of one heteroatom

This approach is infrequently engaged, even though a few examples are present. Chiralauxiliaries are not used in these reactions; in its place the occupant heteroatoms express the nucleophile. The intramolecular addition of an acyloxynitrene to an olefin is an meandering artificial route to amino alcohols via oxazolidinones (Scheme 5).[39] The reaction string starts by formation of an azidoformate from the harmonized allylic alcohol. Thermolyses of this group give abicyclic aziridine, which can be ring-opened to the resultant oxazolidinone.



34 35 36 37 38

The consequent trimmings of oxygen nucleophiles to nitrogen holding molecules are infrequently tried. In the oxa-Michael addition reaction, N-formylnorephedrine added to nitro alkenes, resulted anti-amino alcohols a with excellent selectivities in a four step process (Scheme 6).[40]



39 40 41 42 43

II. RESULT &DISCUSSION

In this paper, a brief assessment on amino alcohol has been offered. Amino alcohols are essential structural moiety present in naturally taking place hydroxyl amino acids like molecules, Lipids and lipid-like Sphingosine, Myrocin molecules which are show signs of immune modulatory activity, gastro defensive activity, and immune stimulatory agents. So it is used clinically as an adjuvant in cancer chemotherapy. Another class of amino alcohol moiety molecules containing sugars are Daunomycin, ElsamicinA, Neomycin B used for Gram negative and Gram-positive bacteria infections. Amino alcohol moiety molecules enclosed man-made pharmacologically active molecules are propranolol, practolol, celiprololhydrochloride, salbutamol, metaprolol are for prove to be useful as antagonists of the calcium receptor I that inhibits parathyroid hormone secretagogues and as β-blocker. A figure of chiral reagents utilize enantiomerically pure amino alcohols as ligands or chiral auxiliaries like Evans auxiliaries', ephedrine derivatives.

A dissimilar type of molecules hold the amino alcohol moiety has been isolated from the natural source, synthesized in pharmaceutical chemistry and used as ligands, chiral auxiliaries. These molecules contain a wide variety of genetic activities. It is the fascinating biological activity as well as the structural complexity of these molecules that have piqued the interest of synthetic molecule chemists and fuelled extensive efforts to build up techniques for the preparation of amino alcohols.

During last 20 years, a numeral of investigate sets have reported a number of synthetic approaches to these 1,2-amino alcohols. Previous synthetic approaches to these 1,2-amino alcohols have been discussed by as long as four complete schemes..

Even though mentioned paths would give the 1,2-amino alcohols in judicious to low yield, a number of confront and some disadvantages still exist, such as tedious reaction conditions, poor regio-selectivity, over alkylation, involvement of energetic intermediates (azides), toxic reagents (hydrazine for phthalimide deprotection), requirement of an additional step for deprotection, and in some cases unsatisfactory selectivity, usage of costly reagents/intermediates, poisonous reagents, the poor stability, and multistep sequences. Therefore it became quite pertinent to develop efficient route for the synthesis of 1, 2-amino alcohols.

CONCLUSION

This research Paper aim is to prepare synthetic organic compounds like Daunomycin, ElsamicinA, Neomycin B used for Gram negative and Gram-positive bacteria infections. Amino alcohol moiety molecules enclosed man-made pharmacologically active molecules are propranolol, practolol, celiprololhydrochloride, salbutamol, metaprolol are for prove to be useful as antagonists of the calcium receptor I that inhibits parathyroid hormone secretagogues.

ACKNOWLEDGMENT

The authors are thankful to the management of AstraZeneca india Pvt Ltd (Bangalore) for providing necessary facilities for this research work

REFERENCES

[1] Coppola, G. M.; Schuster, H. F. Asymmetric Synthesis.Construction of Chiral Molecules Using Amino Acids, Wiley: New York, **1987.**
[2] Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64*, 2852.
[3] Umezawa, H.; Aoyagi, T.; Suda, H.; Hamada, M.; Takeuchi, *T. J. Antibiot*. **1976**, *29*, 97.
[4] Nakamura, H.; Suda, H.; Takita, T.; Auyagi, T.; Umezawa, H.; Iitaka, Y. Y. *Antibiot*. **1976,** 29, 102.
[5] Ino, K.; Goto, S.; Nomura, S.; Isobe, K.-I.; Nawa, A.; Okamoto, T.; Tomoda, Y. *Anticancer Res.* **1995**, *15*, 2081.
[6] Shimojima, Y.; Shirai, T.; Baba, T.; Hayashi, H. *J. Med. Chem*. **1985**, *28*, 3.
[7] Shimojima, Y.; Hayashi, H.; Ooka, T.; Shibukawa, M.; Iitaka, Y. *Tetrahedron* **1984**, *40*, 2519.
[8] Shimojima, Y.; Hayashi, H. *J. Med. Chem.* **1983**, *26*, 1370.
[9] Shimojima, Y.; Hayashi, H.; Ooka, T.; Shibukawa, M.; Iitaka, Y. *Tetrahedron Lett*. **1982**, *23*, 5435.
[10] Shimojima, Y.; Hayashi, H.; Ooka, T.; Shibukawa, M. Agric. *Biol. Chem*. **1982**, *46*, 1823.
[11] Kotsuki, H.; Araki, T.; Miyazaki, A.; Iwasaki, M.; Datta, P. K. *Org. Lett*. **1999**, 1, 499.
[12] Shinozaki, K.; Mizuno, K.; Wakamatsu, H.; Masaki, Y. *Chem. Pharm. Bull*. **1996**, 44, 1823.
[13] Ward, R. A.; Procter, G. *Tetrahedron* **1995**, *51*, 12301.
[14] Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998,** 1075.
[15] Hannun, Y. A.; Linardic, C. M. *Biochem. Biophys. Acta* **1993**, *1154*, 223.
[16] Bagii, J. F.; Kluepfel, D.; St. Jacques, M. *J. Org. Chem*. **1973**, *38*, 1253.
[17] Kluepfel, D.; Bagli, J.; Baker, H.; Charest, M. P.; Kudelski, A.; Sehgal, S. N.; Vezina, C. J. *Antibiot*. **1972**, *25*, 109.
[18] Lown, W. Anthracycline and Anthracendione-Based Anticancer Agents, Elsevier: Amsterdam, **1988**.
[19] Beisler, J. A. *Prog. Med. Chem.* **1982**, *19*, 242.
[20] Leach, B. E.; Calhoun, K. M.; Johnson, L. E.; Teeters, C. M.; Jackson, W. G. *J. Am. Chem. Soc.* **1953,** *75*, 4011.
[21] Sugawara, H.; Tsunakawa, M.; Konishi, M.; Kawaguchi, H.; Krishnan, B.; Cun-heng, H.; Clardy, J. *J. Org. Chem.* **1987**, *52*, 996.
[22] Wright, G. D.; Berghuis, A. M.; Mobashery, S. Aminoglycoside Antibiotics: Structures, Functions and Resistance. *Resolving the Antibiotic Paradox*; Rosen, S. D., Mobashery, S., Eds.; Kluwer Academic/Plenum: New York, **1998**, p 27
[23] Wright, J. L., Gregory, T. F., Heffner, T. G., Mackenzie, R. G., Pugsley, T. A., Meulen, S. V.,and Wise, L. D. Discovery of selective dopamine d4 receptor antagonists: 1-aryloxy-3-(4-aryloxypiperidinyl)-2-propanols. *Bioorg. Med. Chem.*, **1977**, *7*, 1377-1380.
[24] Marquis, R. W., Lago, A. M., Callahan, J. F., Lee-Trout, R. E., Gowen, M., DelMar, E. G.,Van-Wagenen, B. C., Logan, S., Shimizu, S., Fox, J., Nemeth, E. F., Yang, Z., Roethke, T.,Smith, B. R., Ward, K. W., Lee, J., Keenan, R. M., and Bhatnagar, P. Antagonists of the calcium receptor I. Amino alcohol-based parathyroid hormone secretagogues. *J. Med.Chem*., **2009** *52*, 3982-3993.
[25] Apparu, M., Tiba, Y. B., Leo, P., Hamman, S., and Coulombeau, C. Determination of the enantiomeric purity and the configuration of â-amino alcohols using (R)-2-fluorophenylacetic acid (AFPA) and fluorine-19 NMR: application to â-blockers. *Tetrahedron Asymmetry*, **2000**, *11*, 2885-2898.
[26] Joshi, R. A., Gurjar, M. K., and Tripathy, N. K. A new and improved process for celiprolol hydrochloride. *Org. Process Res. Dev.*, **2001** *5*, 176-178.
[27] Ager, D. J.; Prakash, I.; Schaad, D. R. *Chem. Rev*. **1996**, *96*,835.
[28] Studer, A. *Synthesis* **1996**, 793.
[29] Ager, D. J.; Prakash, I.; Schaad, D. R. Aldrichim. *Acta* ,**1997**,*30*, 3.
[30] Parker, K. A.; Ledeboer, M. *W. J. Org. Chem.* **1996,** *61*, 3214.
[31] Fehr, C.; Galindo, *J. Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 1888.
[32] (a) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 2785-2792 (b) Tanaka, Y.; Taniguchi, N.; Uemura, M. *Org.Lett* **2002,** *4***,** 835-838
[33] Kobayashi, S.; Ishitani, H.; Ueno, M. *J. Am. Chem. Soc.* **1998**, *120*, 431-432.
[34] Kumaragurubaran, N.; Juhl, K.; Zhuang, W.; Bøgevig, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2002**, *124*, 6254-6255
[35] Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1531-1546.
[36] Veeresha, G.; Datta, A. *Tetrahedron Lett.* **1997**, *38*, 5223-5224.
[37] (a) Li, G.; Chang, H.-T.; Sharpless, B. K. *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 451. (b) O'Brien, P. *Angew. Chem. Int. Ed. Engl*. **1999**, *38*, 326-329.
[38] Bunnage, M. E.; Chernega, A. N.; Davies, S. G.; Goodwin, C. *J. J. Chem. Soc., Perkin Trans 1*. **1994**, 2373-2384.
[39] Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1997**, *62*, 4449-4456.
[40] Berner, O. M.; Tedeschi, L.; Enders, D. *Eur. J. Org. Chem.* **2002**, 1877-1894.
[41] Hoffman, R. V.; Maslouh, N.; Cervantes-Lee, F. *J. Org. Chem.* **2002**, *67*, 1045-1056.
[42] (a) Lohray, B. B.; Gao, Y.; Sharpless, K. B. *Tetrahedron Lett*. **1989**, 30, 2623-2626.

AUTHORS

First Author –B.Sree Kanth, M.Sc,(Ph.D) , Research Scholar, Rayalaseema University, Kurnool, Ap,India.
bachusreekanth@yahoo.com
Second Author – Dr C. M.Bhaskar Reddy M.Sc, M.Phil, M,Ed, MBA, Ph.D Research Scholar,Rayalaseema University,Kurnool Ap,India. cmbr2008@gmail.com

Third Author – Dr .S.G.Manjunatha M.Sc, Ph.D Research Guide, Rayalaseema University, Kurnool, Ap,India

Correspondence Author – B.Sree Kanth, M.Sc,(Ph.D) , Research Scholar, Rayalaseema University, Kurnool, Ap,India.
bachusreekanth@yahoo.com , 9908118743.