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A STUDY ON (*R*)-2,3-*O*- CYCLO HEXYLEDENE GLYCERALYDE AS A SYNTHETICALLY SIGNIFICANT CHIRAL SYNTHON

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ABSTRACT

The entire series of chemical events required to create a complex, multidimensional molecule from simpler, less expensive, and readily available precursors is known as total synthesis. These processes are frequently seen in natural products or biologically distinct molecules.1. It is generally used to describe a process that is independent of biological processes, setting it apart from semi- or bio-synthesis. The primary goal is to create natural products, dynamic molecules with potential medical use, or chemical substances of potential concern. Usually, the goal is to find a novel synthesis route for a target molecule for which there are already established pathways. Sometimes there isn't a viable path, in which case the chemist insists on discovering one for the first time. Finding novel chemical reactions and novel chemical reagents is the main goal of complete synthesis.

KEY WORDS: *Cyclo Hexyledene Glyceralyde, Chiral Synthon, chemical reactions.*

INTRODUCTION

ASYMMETRIC SYNTHESIS: CHIRALITY

Chemical synthesis involves a process called asymmetric synthesis, which is also referred to as enantioselective synthesis. According to IUPAC, it is a chain of reactions where a chiral substrate is converted into stereo isomeric (enantiomeric or diastereoisomeric) products in unequal proportions.

A molecule is said to be chiral if its atoms are arranged in a way that prevents it from being superimposed on its mirror counterpart. The molecules in the object and mirror image pair share the same components and structural formula. Their interaction is comparable to that of our left and right hands, as Figure 1 above illustrates. This is a crucial idea for stereochemistry and biology. The majority of materials found in mother nature and the biological system are chiral, including nucleic acids, amino acids, which make up proteins, and carbohydrates (sugars, starch, and cellulose).

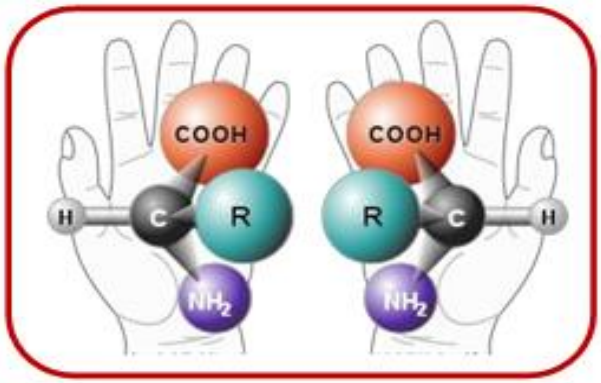

Figure 1 Example of a chiral molecule:

Figure 2 Example of natural chirality:

All the living and nonliving objects are similar but non superimposable (having mirror image relationship).

Usually, only one of the two enantiomers (chiral compounds) may be discovered in living things. Because of this, creatures that eat racemic mixtures, or mixtures of two enantiomers, typically have the ability to digest just one of the enantiomers. As a result, the potencies and effects of the two distinct enantiomers are typically very different. The list of stunning illustrations of chiral chemicals that are biologically active is provided below. In this case, the two enantiomers exhibit entirely different properties.

Lemon peel oil mostly consists of limonene, a colorless liquid aliphatic hydrocarbon that is categorized as a cyclic monoterpene. The D-isomer is used as a flavoring in food manufacture; it is more frequently found in nature as the orange scent. It is also employed as a renewable solvent in cleaning goods and as a precursor to carvone in chemical synthesis. Mint oils contain the less common L-isomer, which smells like turpentine and is piny.4 Whereas caraway seeds contain the D-enantiomer, or S-(+)-carvone, of the chemical carvone, spearmint leaves

have the L-enantiomer, or R-(−)-carvone. Because our olfactory receptors are chiral, most people perceive the two scents differently.

Figure 3 Example of different characteristic with differentchirality: limonene and carvone.

Drug effectiveness: We have shown that drugs are effective. As a selective serotonin reuptake inhibitor, the antidepressant medication Citalopram has been marketed as a racemic combination. Nevertheless, research has demonstrated that the drug's advantageous benefits are exclusively attributed to the (S)- (+) enantiomer.

Medication safety While L-penicillamine is hazardous because it blocks the function of pyridoxine, a necessary vitamin B6, D-penicillamine is utilized in chelation therapy for the treatment of rheumatoid arthritis.

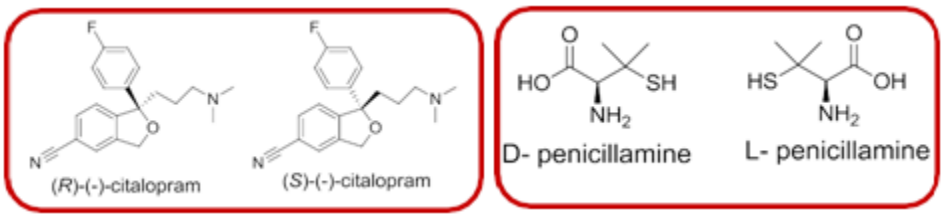

Figure 4 Example of contrasting activity of drugs withdifferent chirality: Citalopram and Penicillamine.

Similarly, chirality is present in many physiologically active compounds, such as carbohydrates and amino acids that are found in nature. Thus, it is easy to draw the conclusion that biological activity, toxicity, pharmacodynamics, and pharmacokinetics have all been found to change significantly between classical enantiomers.Six This situation highlights how important it is to address stereochemistry while developing new drugs.

RESEARCH METHODOLOGY

SYNTHESIS OF OPTICALLY ACTIVE COMPOUNDS

Depending on the sort of starting material employed, there are three primary categories of procedures that can be applied to obtain enantiomerically pure molecules. Using desired chiral beginning materials (chiral-pool material) is one method. An additional possibility involves the clever resolution of a racemic mixture to separate enantiomers.8 Asymmetric synthesis, which involves using a chiral agent to create a chiral center in a prochiral substrate, is the final but most likely synthetically significant method.

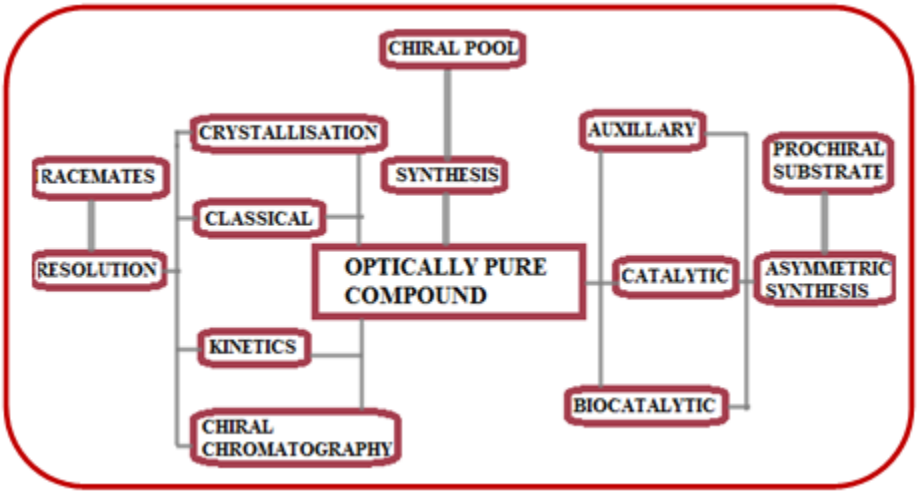

FIGURE 5 SCHEMATIC REPRESENTATION OF DIFFERENT METHODS TO ACHIEVE ENANTIOMERICALLY PURE COMPOUND.

Using the chiral pool technique, optically active raw materials that are easily obtained from the chiral pool—a natural source of chiral molecules—are converted into optically active products. These precursors are then used to synthesize more complex substrates. Because they are affordable raw materials, they are suitable for use in industry. A few essential components of the chiral pool are alkaloids (quinidine, ephedrine, etc.), terpenes ((-)-α-pinene, (-)-β-pinene, (-)-l-menthol, etc.), amino acids (L-glutamic acid, L-phenylalanine, L-proline, etc.), and carbohydrates (D-mannitol, D-glucose, D-sorbitol, etc.).

Using achiral reagents that preserve chirality, a chiral starting material is employed in successive reactions to produce the desired target molecule. One extremely interesting truth can be offered in this context. Approximately 25% of all pharmaceuticals were produced by pure synthetic methods in the early 1990s, with the majority of chiral medications being synthesized from chiral-pool materials. Now, this is no longer the case, with more than 50% of medications coming from other chiral technologies and only roughly 1/4 of pharmaceuticals made from the chiral pool.

D-mannitol is one of the affordable and easily accessible starting materials that has been utilized in asymmetric synthesis for many years. It is a white, crystalline sugar alcohol that is present in living things and has the chemical formula C6H8(OH)6. Since it resembled the food described in the Bible, it was first separated from the excretions of the blossoming ash, which gave rise to the term "manna." These days, it is commercially generated by catalytic hydrogenation of sucrose, fructose, or their syrups. It is also known as mannite and manna sugar.

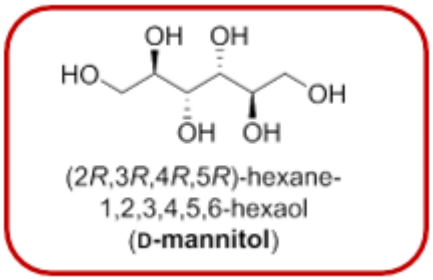

FIGURE 6 CHIRAL SYNTHONS ALKYLIDENEGLYCERALDEHYDES

The chiral synthons alkylideneglyceraldehydes are useful for creating optically active molecules from D-mannitol. The most commonly used of the protected glyceraldehydes is the isopropylidene derivative.12 Contrary to its effectiveness, it possesses difficult-to-handle synthetic features, such as a high water solubility, a propensity to polymerize easily, and instability towards acids. However, there are numerous benefits to the alternative derivative (R)-cyclohexylideneglyceraldehyde, including:

(1) Simple approachability on a multi-gram scale

(2) Considerable reactivity in anhydrous and aqueous medium

3. Not as prone to polymerization

(4) Its ketal functionality is more consistent than that of the corresponding acetonide derivative

(5) Make it possible to achieve a wider range of responses.

There is always need for more research into the potential use of this stable derivative of the moderate variety of chiral hydroxyl aldehyde in the synthesis of advantageous bioactive compounds under synthetic supervision, given its advantages and ease of accessibility. Because this molecule has been effectively utilized as a synthon for the

preparation of various clinically necessary chiral compounds in several places throughout the thesis, we have chosen to offer an ephemeral review of this important molecule.

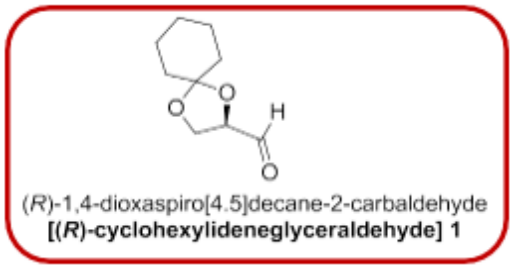

FIGURE 7 (R)-CYCLOHEXYLIDENEGLYCERALDEHYDE 1

Various synthesises have used (R)-cyclohexylideneglyceraldehyde 1 as a starting material.15 Over the past few years, Compound 1 has proven to be an incredibly flexible, easily obtainable, and inexpensive chiral template for a number of enantioselective transformations. In addition to providing significant steric bias when adding organometallics to its aldehyde functional group, the cyclohexylidene moiety of aldehyde 1 also guarantees the peaceful separation of the resulting epimeric carbinols by standard column chromatography. Several structural entities, including alkanetriols, ribofuranoses, γ-lactones, δ-lactones, 2,5-disubstituted tetrahydrofurans, and other biologically powerful moieties, have been successfully constructed using Compound 1. Additionally, it has been used to prepare a variety of chemical motifs, such as those employed extensively in organic synthesis, such as fucosidase, glycosidase, and DNA polymerase inhibitor, as well as certain epoxy diols.

RESULTS AND DISCUSSION

This is a historical overview of various notable syntheses during the last thirty years that begin with (R)-cyclohexylideneglyceraldehyde 1 as the starting chiral material. The reviews begin in 1995. Grignard reaction has been used to add different nucleophiles to a variety of aldehydes; there are several examples of this phenomena. In 1995, Chattopadhyay et al. provided testimony regarding the synthesis of homoallylic and homopropargylic alcohols, which are the precursors of the unsaturated fatty acid (-)-coriolic acid. Grignard addition to 1 produced diastereoalcohols that could be distinguished by column chromatography. Benzoylation of 2 (one of the two diastereomeric alcohols) yielded 3. Following the cyclohexyl group in 3's deprotection in an acidic medium, diol 4 was produced. This converted to aldehyde 5, which functions as a bridge for the manufacture of cariolic acid 6, a regular defense compound that combats the fungal illness rice blast..

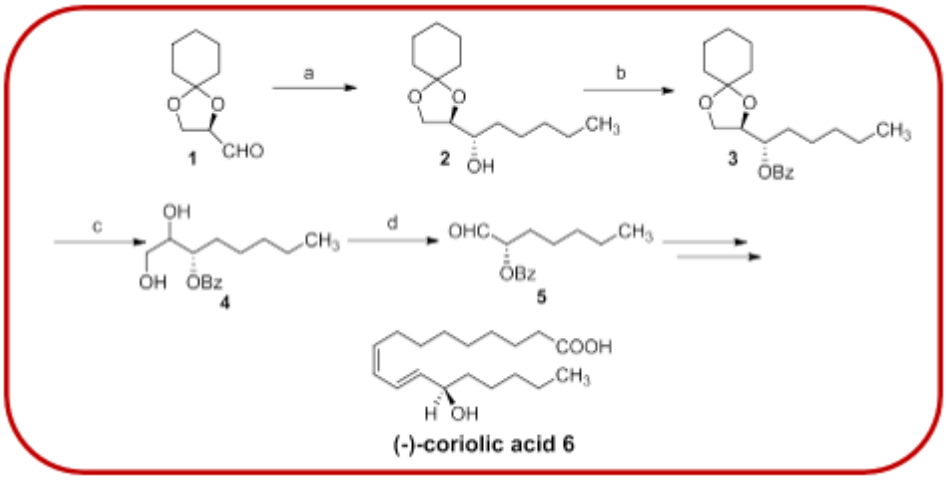

Figure-8 ***REAGENTS AND CONDITIONS*****: (A) (I) CH3(CH2)4MGBR, THF, (II) COLUMN CHROMATOGRAPHY; (B) PHCOCL, PYRIDINE; (C) CF3COOH, H2O, 0°C; (D) NAIO4.**

Using Luche's method, Chattopadhyay et al. (16a) employed Zn-mediated allylation and propargylation of (R)-2,3-O-cyclohexylideneglyceraldehyde (1) in an aqueous medium to produce the anti-homallylic 8 and homopropargylic 13 alcohols with good yield and strong stereoselectivity. Under similar circumstances, crotylation of 1 can yield significant amounts of erythro-10 and threo-11 alcohols. Each time, column chromatography allows for the distinct separation of the diastereomeric alcohols. Regarding advantageous chemical modification of its functions In addition to other possibly helpful bioactive compounds, compound 13 provided the (S)-enantiomer of (R)-15 and a beneficial synthon of LTB4 inhibitor (Leukotriene B4-potent pro-inflammatory action). Compound 8 yielded a clearly functionalized triol derivative 17 upon chemical amplification.

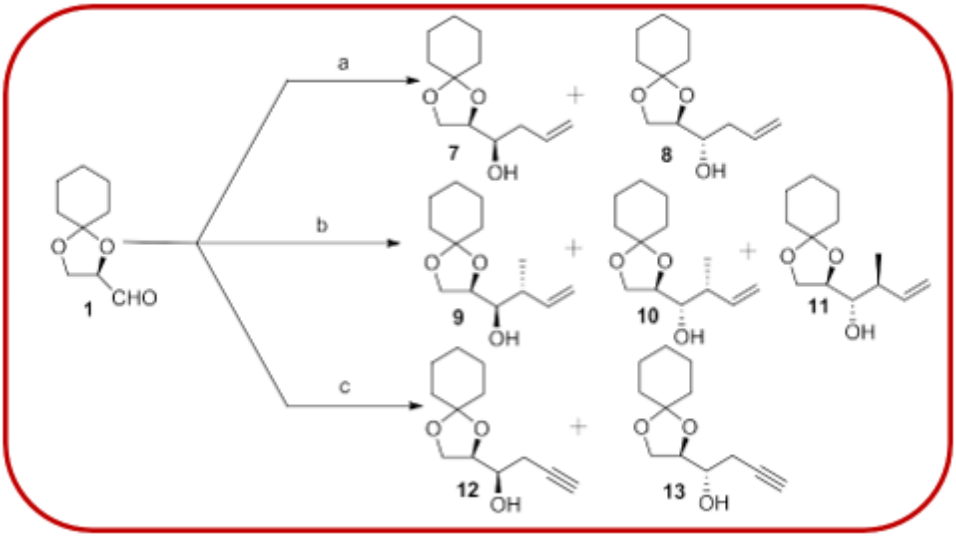

FIGURE-9 *REAGENTS AND CONDITIONS*: (A) (I) ALLYL BROMIDE/ ZN, (II) AQUEOUS NH4CL; (B) (I) CROTYL BROMIDE/ ZN, (II) AQUEOUS NH4CL; (C) (I) PROPARGYL BROMIDE/ ZN, (II) AQUEOUS NH4CL.

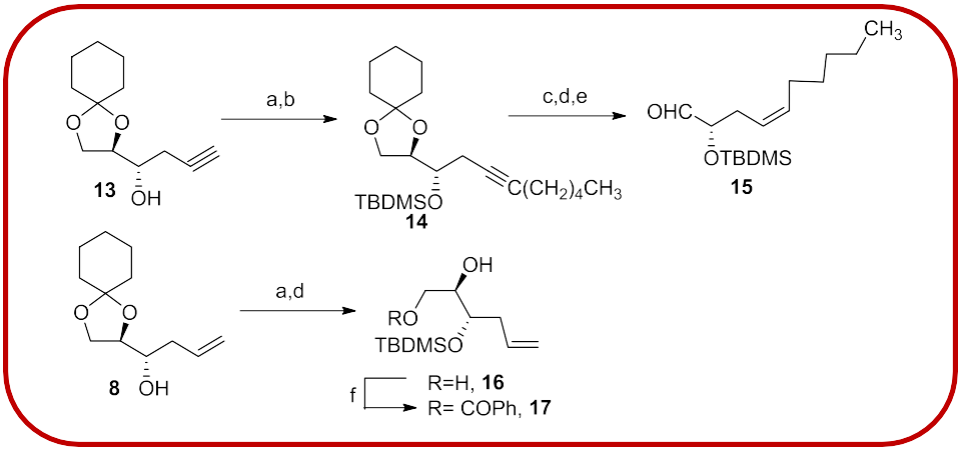

FIGURE-10 *REAGENTS AND CONDITIONS*: (A) TBDMSCL/ DMF; (B) *N*-BULI/ *N*-BROMOPENTANE; (C) H2/ P(2)-NI (BOROHYDRIDE-REDUCED NICKEL) CATALYST; (D) CF3CO2H/ H2O; (E) NAIO4; (F) PHCOCN/ TEA.

By reacting alkyl-cyanocuprates with 3, 3-dibenzyloxy-1-tributylstannylprop-1-ene in the presence of boron trifluoride, Fliegel et al. (21) report that compound benzyloxyallyltributyltins 19 was produced in an effective yield. They interacted with several Lewis acids when cyclohexylideneglyceraldehyde 1 was present. Genuine aldopentoses 21 can be compared to the achieved diastereomeric adducts that were unquestionably recognized

following the deprotection-ozonolysis sequence. The processes and the relationship between the reagent configuration and the allylstannation reaction's selectivity are well covered in this paper.

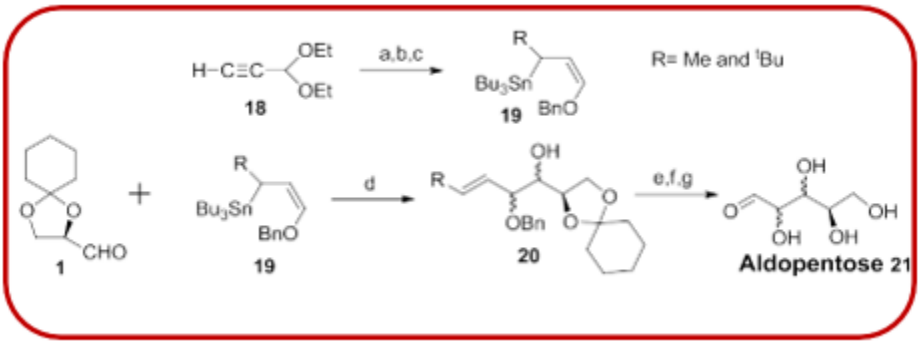

FIGURE-11 *REAGENTS AND CONDITIONS*: (A) $PHCH_2OH$/ PTSA, HEXANE;(B) $BU_3SN(BU)CUCNLI_2$, THF, -78°C; (C) RCU(CN)MGCL, BF_3. ET_2O, ETHER, -78°C- -30°C; (D) $BF_3.ET_2O$ (3 EQ.), DCM, -78 °C; (E) CF_3COOH/ H_2O, 50 °C; (F) O_3, ME_2S; (G) H_2, PD/C, MEOH.

Compostella et al. (2002) reported using a stereo convergent approach to describe the chemoenzymatic synthesis of 3-O-benzoyl azidosphingosine 27. Compound 1 was nucleophilically treated with the Grignard reagent of 1-pentadecyne, yielding a mixture of diastereoisomeric propargylic alcohols 22. Candida Antarctica lipase aided in the subsequent enzymatic separation of these diastereoisomers. The specified chemical 27 was obtained in a reasonably high overall yield of around 30% through the application of a chloromesylate leaving group in the Mitsunobu inversion, which was performed to the incorrect diastereoisomer.

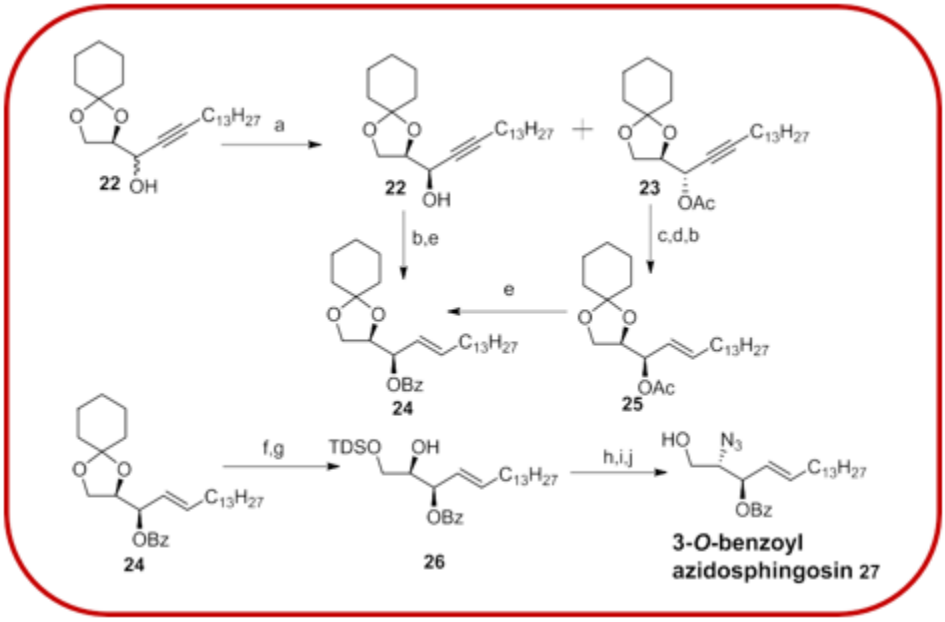

FIGURE-12 *REAGENTS AND CONDITIONS*: (A) LCA (LIPASE FROM *CANDIDA ANTARCTICA*), VINYL ACETATE, CYCLOHEXANE, 40 °C; (B) LIALH4, THF, 40 °C; (C) MEONA, MEOH; (D) ACOH, PPH3, DIAD, PYRIDINE, THF; (E) BZCL, PYRIDINE, DCM; (F) TFA, H2O, 0 °C; (G) TDSCL (TDS= THEXYLDIMETHYLSILYL), PYRIDINE; (H) MSCL, PY; (I) NAN3, DMF, 85 °C; (J) 2% AQ HF, THF, MECN.

A broad and proficient technique for producing α-monofuoromethylene phosphonates and sn-1 and sn-2-O-methylated LPA analogues (anti-apoptotic activity; sn-signifies stereospecific numbering scheme) was established by Xu et al. in 2003.23 Additionally, a novel technique for the selective etherification of 1,2-diols was created. A broad range of reactions from cells and tissues are triggered by lysophosphatidic acid 31 (LPA, 1- or 2-acyl-sn-glycerol 3-phosphate), including calcium mobilization, antiapoptotic variations in cell shape and motility, and mitogenesis.

CONCLUSION

In this article, this brief review explores the versatility of (R)-2,3-cyclohexylideneglyceraldehyde 1 as a valuable chiral building block and its wide range of uses in various bioactive compounds. In the following research, we have detailed the various uses of this method in creating specific molecules with biological significance, including

the diastereomers of whisky and cognac lactones. Chiron's method was employed to synthesize highly pure (R)- and (S)-1-(2,6-dimethylphenoxy) propan-2-ol, which serve as crucial building blocks for the synthesis of class I-B antiarrhythmic oral drugs (S)- and (R)-mexiletines, respectively. In research, we have demonstrated the stereochemical importance and versatility of compound 1. Based on this compound, we have developed two different types of chiral intermediates: a pair of diastereomers of a saturated ester intermediate, and a tosyl intermediate. Four stereoisomers of cis- and trans- whisky and cognac lactones have been synthesized from these two diastereomers of ester, showcasing the expertise of a chemist. Two enantiomers of mexiletine have been synthesized from a shared tosyl intermediate.

Pharmaceutical ingredients, scents, and flavors are often sought after for theirchirality. For synthetic chemists, (S)-γ-Hydroxymethyl-α,β-butenolide (HBO) is a chiral (5H)-furanone that offers a polarized double bond, a lactone ring, and a primary alcohol. For forty years, this molecule has been employed in numerous synthetic pathways leading to natural and/or bioactive compounds. Its own synthesis, which is always done from biosourced products, has also advanced greatly and is now feasible on a big scale and through the use of green chemistry concepts. The synthesis, reactivity, and applications of HBO are examined in this review.

REFERENCES

- M. Eichelbaum, A. S. Gross, *Adv. Drug Res*. **1996**, *28*, 1-64;
- R. R. Shah, J. M. Midgley, S. K. Branch, *Toxicol. Rev*. **1998**, *17*, 145-190.
- J. M. Hawkins, T. J. N. Watson, *Angew. Chem. Int. Ed.* **2004**, *43*, 3224-3228.
- E. Fogassy, M. Nogradi, D. Kozma, G. Egri, E. Palovics, V. Kiss, *Org. Biomol. Chem.* **2006**, *4*, 3011-3030.
- R. H. Crabtree, Handbook of Green Chemistry: Biocatalysis. Weinheim: Wiley-VCH, **2009**, *3*, 173.
- E. Schwarz, Sugar alcohols: Mannitol. *In Ullman's Encyclopedia of Industrial Chemistry*, eds. B. Elvers, S. Hawkins and W. Russey, 5th ed., volume A25, VCH, Weinheim **1994**, 423-426.
- H. Ojamo, H. Koivikko, H. Heikkila, *Patent application WO 0004181*, 27. 1. **2000**.
- H. Ohrui, *J. Syn. Org. Chem. Jpn*. **1981,** *39*, 275-278; (b) T.
- Sugiyama, K. Yamashita, *Agric. Biol. Chem*. **1980**, *44*, 1983-1984;
- T. Sugiyama, M. Watanabe, T. Sassa, K. Yamashita, *Agric. Biol. Chem*. **1983,** *47*, 2411-2413; (d) A. Tanaka, K. Yamashita, *Agric. Biol. Chem*. **1980**, *44*, 199-202.
- Chattopadhyay, V. R. Mamdapur, *J. Org. Chem*. **1995**, *60*, 585-587.
- J. Jurczak, S. Pikul, T. Bauer, *Tetrahedron* **1986**, *42*, 447-488.

- Chattopadhyay, P. Vichare, B. Dhotare, *Tetrahedron Lett*. **2007**, *48*, 2871-2873; (b) A. Chattopadhyay, D. Goswami, B. Dhotare, *Tetrahedron Lett*. **2006**, *47*, 4701-4705.
- A. Chattopadhyay, *J. Org. Chem*. **1996**, *61*, 6104-6107; (b) A. Chattopadhyay, B. Dhotare, S. A. Hassarajani, *J. Org. Chem*. **1999**, *64*, 6874-6878; (c) B. Dhotare, A. Salaskar, A. Chattopadhyay, *Synthesis* **2003**, 2571-2575.