Isomannide and Derivatives. Chemical and Pharmaceutical Applications

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Abstract: Isomannide, 1,4:3,6-dianhydro-D-mannitol, is a commercially available chiral carbohydrate derived from ready dehydration of naturally occurring D-mannitol. This compound and its derivatives have been widely used in many areas such as building blocks for polymers synthesis, pharmaceutically important compounds, catalysts in asymmetric synthesis, chiral auxiliaries, and recently, in the synthesis of ionic liquids. In this review we show examples of these applications of isomannide and derivatives.

Keywords: Isomannide, chiral auxiliaries, catalysts, protease.

INTRODUCTION

Isomannide (**1**), 1,4:3,6-dianhydro-D-mannitol, is a renewable, inexpensive and commercially available chiral carbohydrate derived from ready dehydration of naturally occurring D-mannitol [1]. It is obtained in large amounts as waste during the processing of corn oil. Isomannide was described for the first time by Fauconnier in 1882 and its structure was elucidated in 1945 by Fletcher and Wiggins (Fig. **1**) [1-4]. Isomannide is a structurally rigid bicyclic molecule containing a C_2 axis of symmetry along with two hydroxyl groups at the *endo* position which makes it an attractive biologically derived scaffold for synthetic applications [5-7]. Such applications include the ability to use isomannide as a starting material for pharmaceutically useful derivatives. Already, it is used as a phase transfer catalyst (PTC) in asymmetric synthesis, as a chiral ligand and auxiliary, in the synthesis of chiral ionic liquids (CILs), and as monomers for the synthesis of biodegradable polymers. In this review we will illustrate examples of these applications of isomannide and its derivatives.

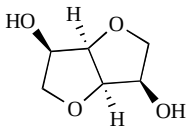

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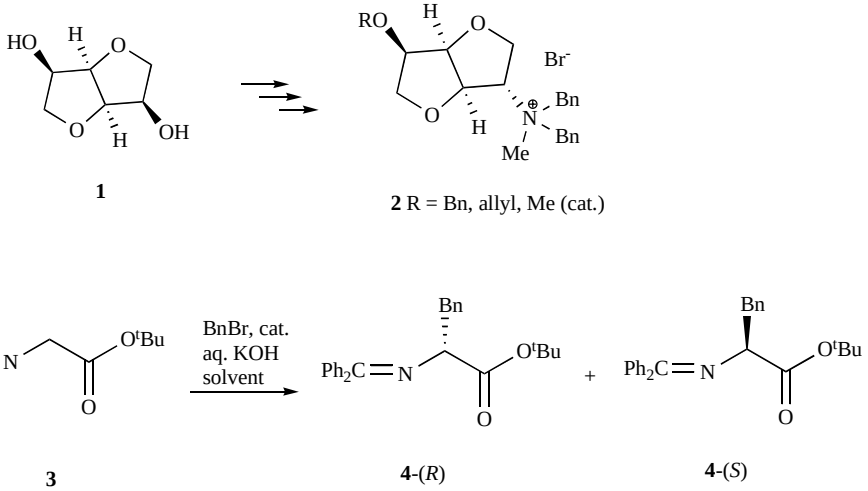
Fig. (1). Structure of Isomannide.

Catalytic Agents

Catalytic asymmetric phase-transfer reactions constitute an important methodology in synthetic chemistry, therefore the creation of new PTCs is a very alluring area of investigation. Nevertheless, research on the synthesis of PTCs, based on structurally rigid dioxabicyclo systems has received little attention. Ramachandran and co-workers reported the synthesis of isomannide and isosorbide derivatives and their use as PTC. These derivatives were used to prepare the quaternary ammonium salts **2** in good yields which were used in an asymmetric alkylation reaction with the imine **3**



1 **2** R = Bn, allyl, Me (cat.)

3 **4**-(*R*) **4**-(*S*)

Scheme 1.

using benzyl bromide as alkylating agent, as shown in Scheme **1** for the isomannide. The results showed the new PTCs to be effective with enantioselectivity in the range of 70:30 (*S*:*R*) [5].

Isomannide has also been utilized in the preparation of novel homochiral bis-imine ligands **5** from the reaction of its bis-amine derivative with aromatic aldehydes. In this case **5** was stirred with

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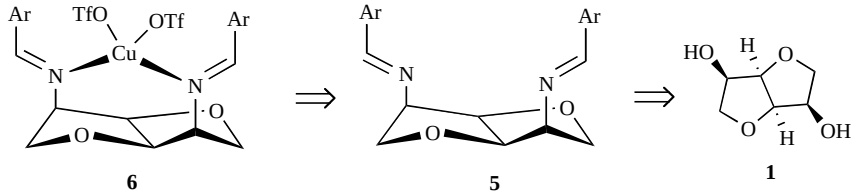
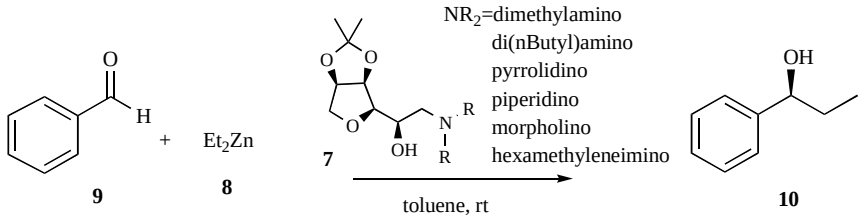


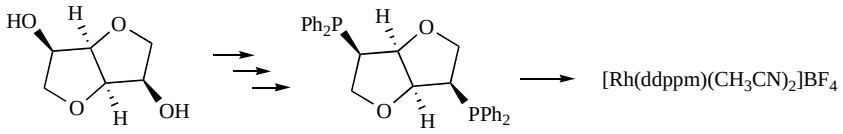
6 **5** **1**

Scheme 2.



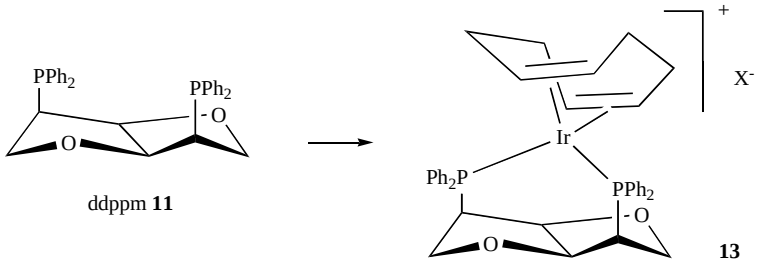
9 **8** **7** **10**

Scheme 3.



1 ddppm **11** **12**

Scheme 4.



ddppm **11** **13**

Scheme 5.

copper(II) triflate to produce the catalyst **6**. These ligands have been used in asymmetric Diels-Alder reactions of cyclopentadiene and N-*tert*-crotonoylooxazolidinone. The aryl substitution pattern plays a crucial role in governing the *endo-exo* selectivity of the reaction (Scheme **2**) [6].

Cho and co-workers have described a method for the preparation of chiral *β*-amino alcohols **7**, starting from **1** as well as their application for the catalytic ethylation of aldehydes, such as benzaldehyde (**9**), with diethylzinc (**8**) (Scheme **3**) [7]. The absolute configuration of the alcohol **10** was identified as *S* enantiomer.

Carcedo and co-workers were the first to describe the synthesis of 1,4:3,6-dianhydro-2,5-di-deoxy-2,5-bis(diphenyl-phosphino)-L-mannitol (ddppm) (**11)**, a di-*endo* phosphine derivative of isomannide. The efficient chirality transfer from ddppm was anticipated due to the rigid backbone conformation, its chelating nature, and the presence of a C_2 axis. The rhodium complex of ddppm **12** was obtained and employed in the asymmetric olefin hydrogenation (Scheme **4**) [8].

The same group has prepared a new ddppm complex with iridium **13**, which has been employed as a catalyst in the asymmetric hydrogenation of a variety of imine substrates (Scheme **5**). Contrary to other known iridium catalysts with ddppm, the new complexes were efficient catalysts under an atmospheric hydrogen pressure. The resulting secondary amines were obtained in high yield and enantioselectivity (80-94% *ee*) [9].

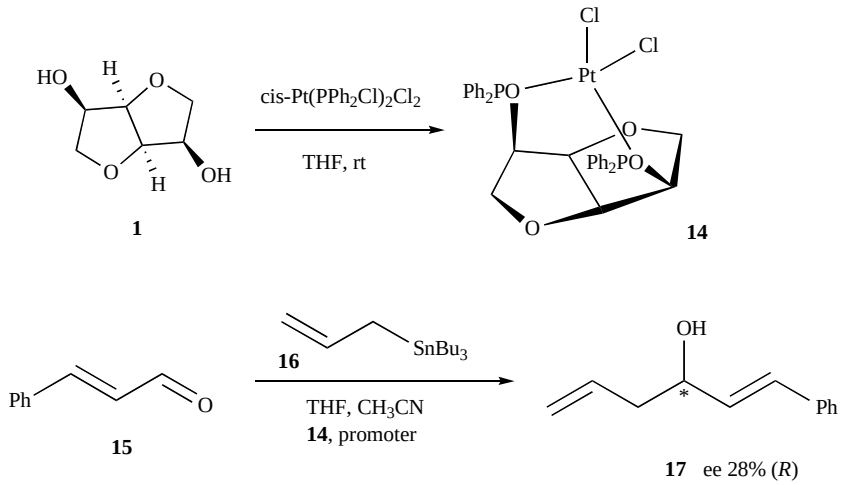
More recently, isomannide has been utilized to prepare a platinum phosphinite complex **14** in order to catalyze the allylation of cinnamaldehyde (**15**) with allyltributyltin (**16**). This complex, and others made using chiral diols, has been characterized by X-ray diffraction direction studies (Scheme **6**). The allylation reactions yielded different enantiomeric excesses, greater when reactions were carried out with phosphinite ligands possessing hydrogen bond donors or acceptors [10].

Monomers and Polymers

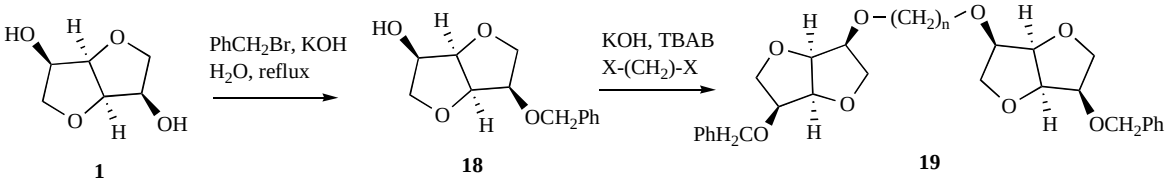
Chiral diols have also attracted interest as monomers for the synthesis of various polycondensates, such as polyethers, polyurethanes, polyamides and others.

The use of isomannide in macromolecular chemistry is a relatively new area that has yet to be fully exploited; however, Loupy and co-workers have described the synthesis of diols linked by ether functionalities as monomers in various polymerization reactions. Alkylation reactions have been utilized under microwave-assisted PTC conditions with TBAB as phase transfer agent in economical and mild conditions (Scheme **7**) [11,12].

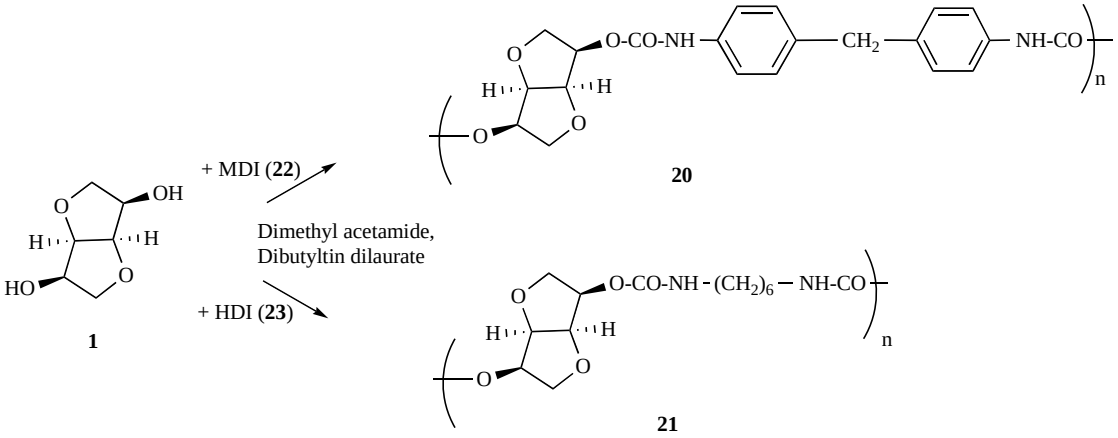
Microwave assisted synthesis has also been used in polycondensation processes for the synthesis of new aliphatic polyethers of dianhydro-hexitols. In comparison with conventional heating, the reaction time was reduced from 24 h to 30 min. with higher yields of the polyethers [13].



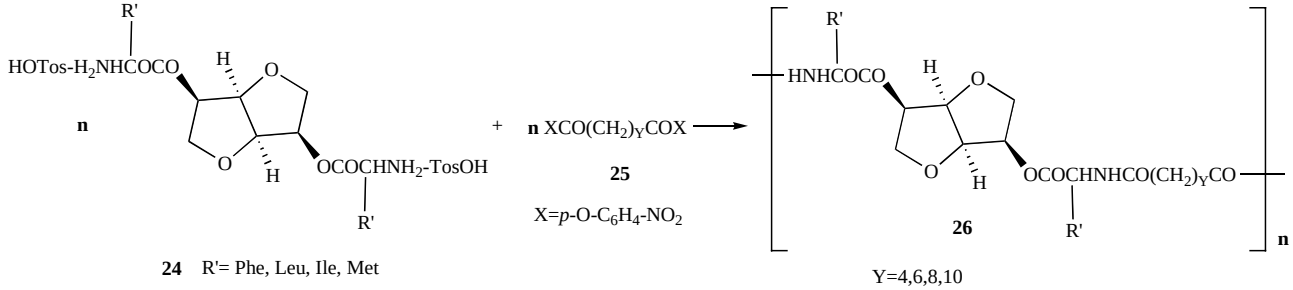
Scheme 6.



Scheme 7.



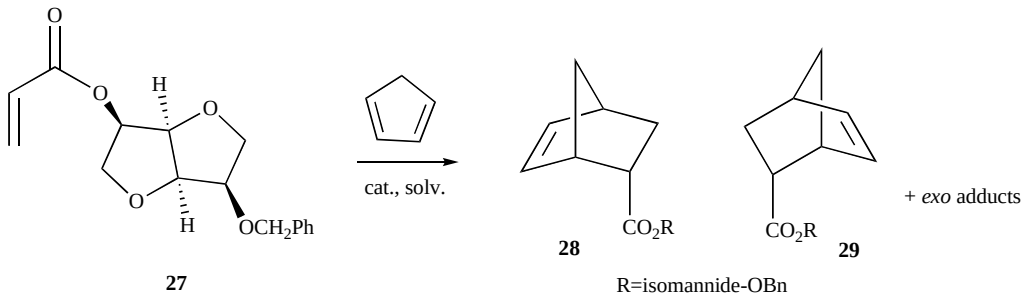
Scheme 8.



Scheme 9.

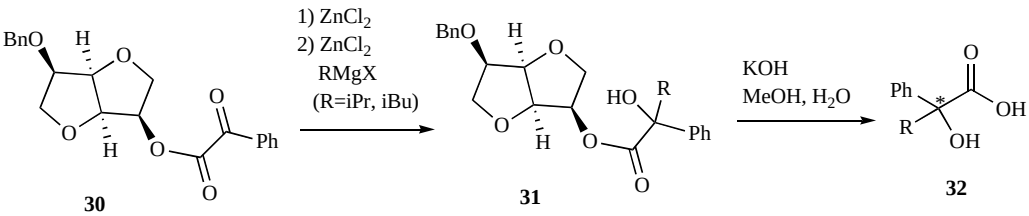
Recently, matrix-assisted laser desorption/ionization (MALDI) mass spectrometry and NMR spectroscopy have been utilized in the characterization of novel poly-(ether-urethane)s, e.g. **20** and **21,** from various diols derived from starch and diisocyanate. The polyurethanes soft and hard blocks were prepared by polyaddition of isomannide (**1**) with 4,4-diphenylmethane diisocyanate (MDI) (**22**) and or hexane-1,6-diisocyanate (HDI) (**23**) (Scheme **8**) [14].

A new class of biodegradable poly(ester-amide)s has been prepared from esterification of isomannide with α-amino acids. The amino groups liberated were polycondensed with *p*-nitrophanyl esters of aliphatic dicarboxylic acids. Preliminary studies showed enzymatic degradation by the use of chymotrypsin or lipase (Scheme **9**) [15]. This group has previously published a review of chiral condensation polymers based on sugar diols as isomannide [16].



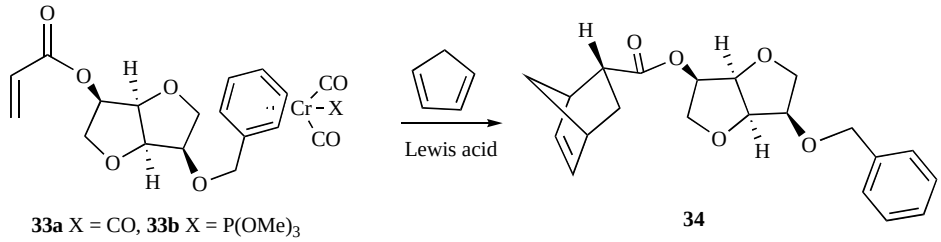
27 **28** **29**

Scheme 10.



30 **31** **32**

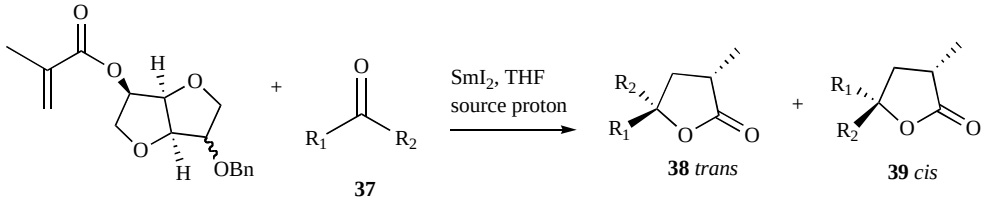
Scheme 11.



33a X = CO, **33b** X = $P(OMe)_3$
33c X = $P(OEt)_3$,**33d** X = $P(OPh)_3$

34

Scheme 12.



35 OBn
36 OBn

37

R_1=Ph, *p*-OMe-C_6H_4, 2-naphthyl, 3,4-methylenedioxy-phenyl
R_2=Me, Et

38 *trans* **39** *cis*

Scheme 13.

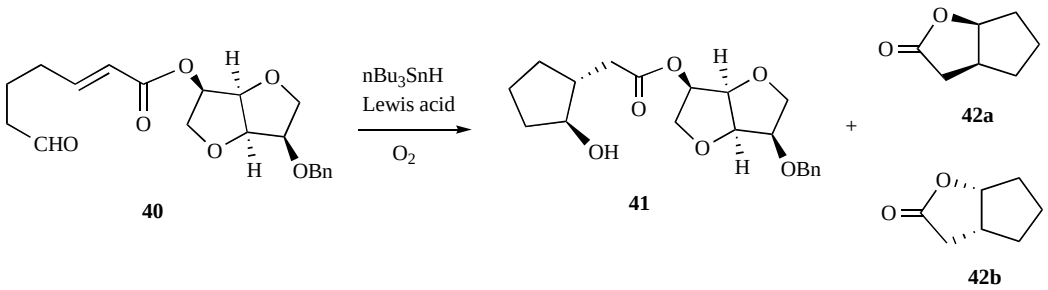
Chiral Auxiliaries

Sugar diols such as isomannide have been used as chiral auxiliaries in a number of reactions including alkylation, Diels-Alder reaction, asymmetric hydrogenation, etc. Loupy and co-workers have shown Diels-Alder reactions of acrylate esters from monobenzylated isomannide **27** and cyclopentadiene promoted by Lewis acid. The authors discussed how this cycloaddition reaction might be influenced by π-interactions, which help to account for the levels of asymmetric induction (Scheme **10**) [6, 17].

Chiral tertiary α-hydroxy acids are important building blocks and synthetic intermediates for the synthesis of biological active molecules. The preparation of new chiral auxiliaries for the synthesis of enantiopure α-hydroxy acids was also explored by Loupy and co-workers. Here, diastereoselective additions of organozinc reagents with the derived phenylglyoxylates **30** afforded the desired compounds with 60-99% ee following saponification (Scheme **11**) [18].

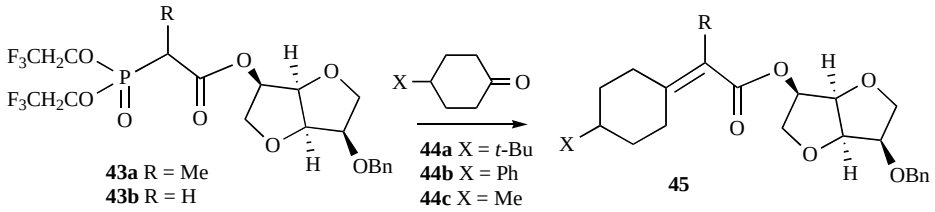
In order to investigate and attempt modulation of π-interactions in the cycloaddition of **27** with cyclopentadiene, a series of η^6 arene chromium carbonyl complexes **33** from isomannide was prepared and employed as reactants in the Diels-Alder reaction (Scheme **12**). It is interesting to note that with the π-deficient complexes **33a** the diastereocontrol is enhanced over **27**, suggesting a combination of steric and electronic factors [19,20].

Lin and co-workers have explored the chemistry of the construction of chiral butyrolactones using easily obtained and inexpensive chiral auxiliaries of isomannide and isosorbide [21]. The authors demonstrated the SmI_2-induced reductive coupling of chiral 2-alkyl acrylates **35** and **36**, with various ketones in the presence of a proton source that yielded the chiral α,γ-substituted γ-butyrolactones. The products were efficiently prepared and exhibited excellent *ee* values of their *trans* diastereoisomers **38** (Scheme **13**) [22].



40 **41** **42a** **42b**

Scheme 14.

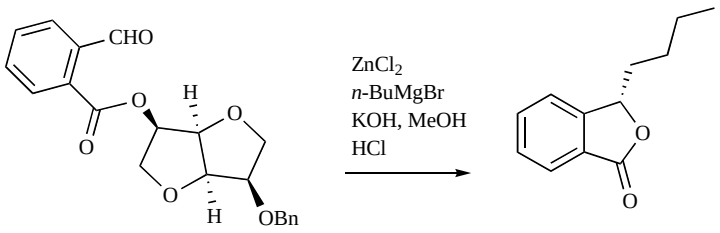


43a R = Me
43b R = H

44a X = *t*-Bu
44b X = Ph
44c X = Me

45

Scheme 15.



47 *S*-NBP **46**

Scheme 16.

For more than two decades tributyltin hydride has been used in a diversity array of free radical cyclization reactions. *O*-stannyl ketyl is very useful intermediate as it differs from other radicals in a variety of facets, including stability and reactivity. One means of improving diastereoselectivity in free radical reactions has been the exploitation of a combination of Lewis acids and chiral auxiliaries. A chiral carbohydrate from isomannide affords an excellent precursor for such reactions due to its highly oxygenated structure providing multiple sites for metal chelation. Hence, *O*-stannyl ketyl aldehyde-alkene cyclization of the derivative **40** has been performed using zinc chloride, $MgBr_2$-OEt_2 and CuOTf as Lewis acid (Scheme **14**). The reactions yielded a high diastereoisomeric ratio of 100:1 for **41**. In addition, the lactones **42a** and **42b** were formed in smaller amounts [23].

Sano and co-workers examined the enantioselective Horner-Wadsworth-Emmons (HWE) reaction with an axis of chirality [24,25]. The authors demonstrated the asymmetric HWE reaction of a reagent bearing *O*-benzylisomannide **43** with symmetric prochiral ketones **44** using $Sn(OSO_2CF_3)_2$ and *N*-ethylpiperidine (Scheme **15**). An excellent de of 99% was achieved by HWE reaction of **43a** with ketone **44c** [26].

The asymmetric synthesis of 3-*n*-butylphthalide (NBP) **46**, a natural product with important pharmacological properties (including the inhibition of platelet aggregation and reduction of thrombus formation) has been limited due to the difficult and expensive access of chiral auxiliaries and catalysts. Based on such synthetic hurdles, Min and co-workers described a facile synthesis of NBP using readily available and inexpensive auxiliaries such isomannide [27]. The reaction employing isomannide, illustrated in Scheme **16**, involves the diastereoselective addition of dibutylzinc to an aromatic aldehyde **47** derived from **1** yielding *S*-NBP (**46**) in 98% ee.

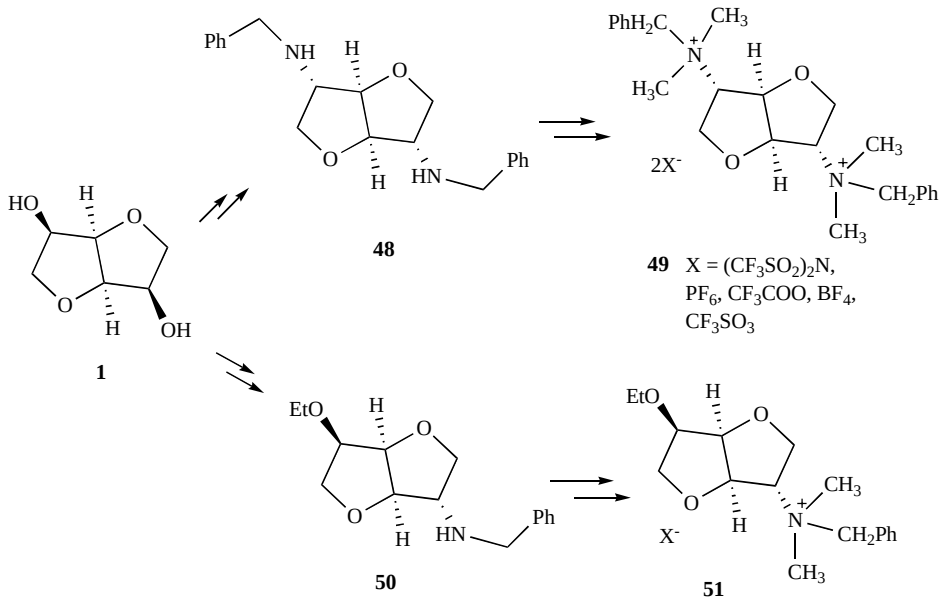
Chiral Ionic Liquids (CILs)

Ionic liquids (ILs) have shown considerable application in chemistry as potential candidate to replace conventional volatile organic solvents due to their advantageous characteristics as negligible vapor pressure, high thermal stability and recyclability, etc [28]. They have found promising applications in asymmetric synthesis, chromatography, polymerization and other various reactions [29,30]. Although the synthesis of CILs requires substrates from a chiral pool, carbohydrate-based substrates is a very novel approach. Malhotra and co-workers have elegantly explored the synthesis of CILs derived from isomannide and their use in the chiral resolution of Mosher`s acid salt. The synthesis of mono **51** and bis(ammonium) **49** CILs from **1** is shown in Scheme **17**, and the results of these experiments illustrate their efficiencies as chiral shift reagents and chiral solvents/catalysts in asymmetric synthesis [31,32].

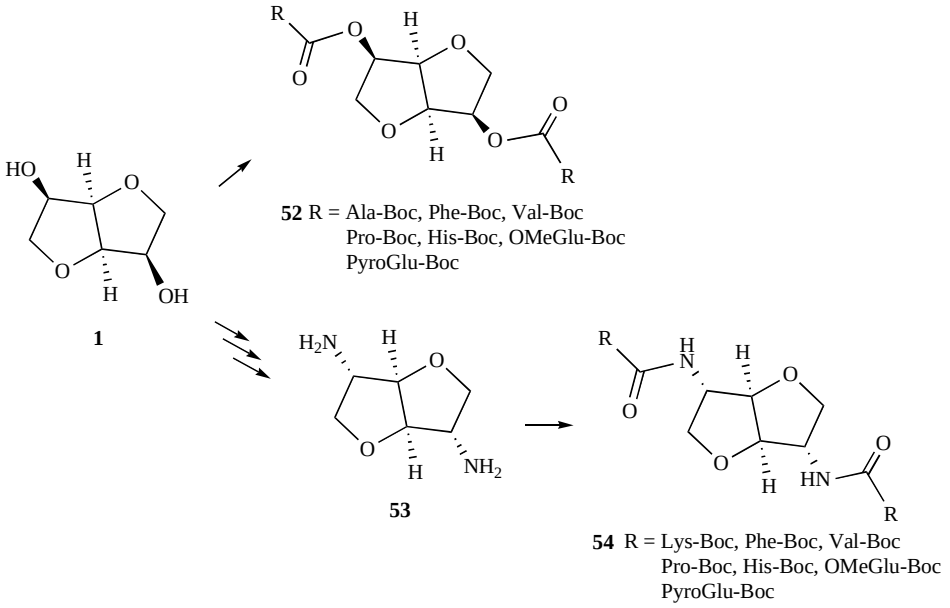
Pharmacological Agents

Proteases are enzymes that catalyze the hydrolysis of peptide bonds and are the most well known class of proteolytic enzymes. The enzymes are sub-divided in aspartylprotease, cysteine protease, serine protease, threonine protease or metalloprotease. The serine protease family is the largest of all protease families. It has a classical catalytic triad consisting of serine, histidine, and aspartate in the active site. Proteases are therefore important drug targets in the pharmaceutical industry [33,34].

Hepatitis C, Dengue and West Nile virus are among of the most important flaviviruses that share one important serine protease. On this view, Muri and co-workers have examined novel compounds as potential inhibitors of serine proteases for the therapy of Dengue and Hepatitis C. These investigators have employed isomannide as



Scheme 17.



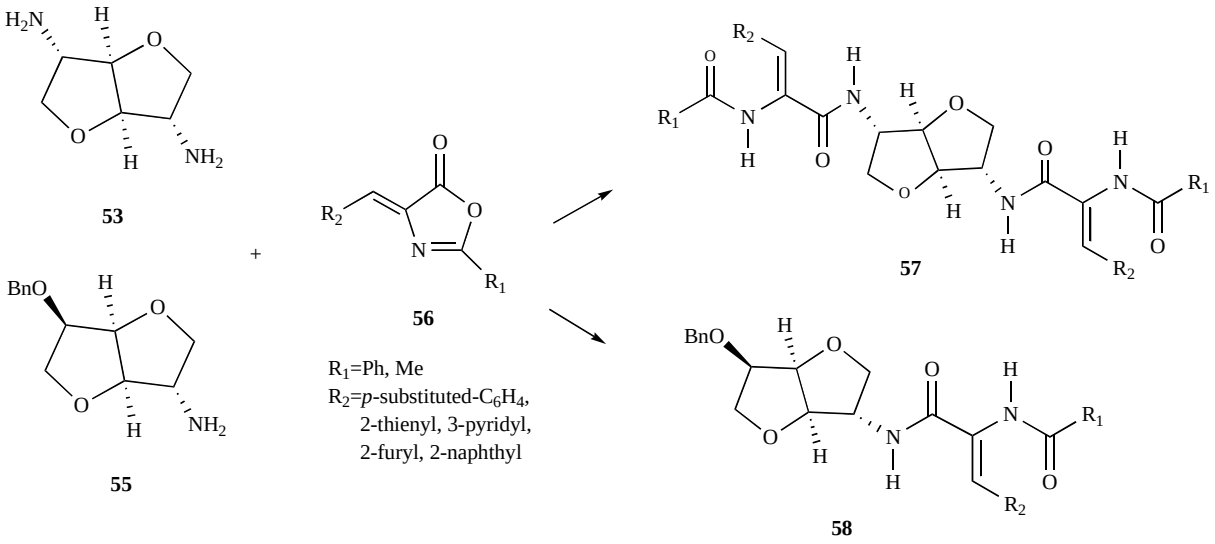
Scheme 18.

the core unit of the peptide mimetic compounds, rationalizing its use as a structural analog with cyclic rigid dipeptides and a C_2 symmetry providing a rigid scaffold. Initially, these researchers reported the synthesis of a series of *N*-*t*-Boc-amino acid esters of isomannide **52**, which had been based on computational modeling experiments. The results indicated a requirement of basic residues at P1 position leading to the synthesis of a new series of pseudo-peptides **54** [35], through a coupling reaction of bis-amide **53** and several amino acids Boc-protected (Scheme **18**) [36].

In an ongoing effort to construct new serine protease inhibitors using isomannide as scaffold, Muri and co-workers have described new symmetric and asymmetric isomannide derivatives from the respective reactions of bis-amine **53** and the *O*-benzylated amine **55** with different oxazolones (**56**) (Scheme **19**). These compounds have been evaluated using the HCV replicon-based assay. The most active compound **58** (R_1= -Ph, R_2 = thiophene) has demonstrated significant anti-HCV activity with IC_{50} value of 35 μM [37,38].

The serine protease factor Xa (fXa) plays a central role in the coagulation cascade and has been a very attractive target for anti-thrombotic agents. The active site of fXa is well described showing a hydrophobic S1 pocket and an aryl binding S4 pocket, which facilitate a rational inhibitor design. Vogler and co-workers have designed and synthesized a series of dianhydrohexitol-based benzamidine derivatives as fXa isomannide-based inhibitors, e.g. **59** and **60**, which have the advantage of combining high rigidity with stereochemical bias. The benzamidine residue, recognized by an asp189 located at the S1 pocket and the biphenyl group in the S4 pocket were found to be exceptional ligands for fXa inhibition (Fig. **2**) [39,40].

Protein phosphatases are key regulators of innumerable biological process including diabetes and cancer. Recently, based on biology-oriented synthesis (BIOS), a library of new phosphatases inhibitors has been synthesized inspired on furanodictine scaffold **61**



Scheme 19.

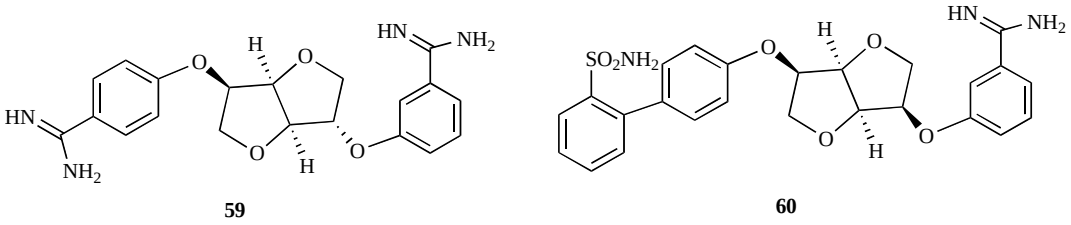


Fig. (2). FXa isomannide-based benzamidine inhibitors.

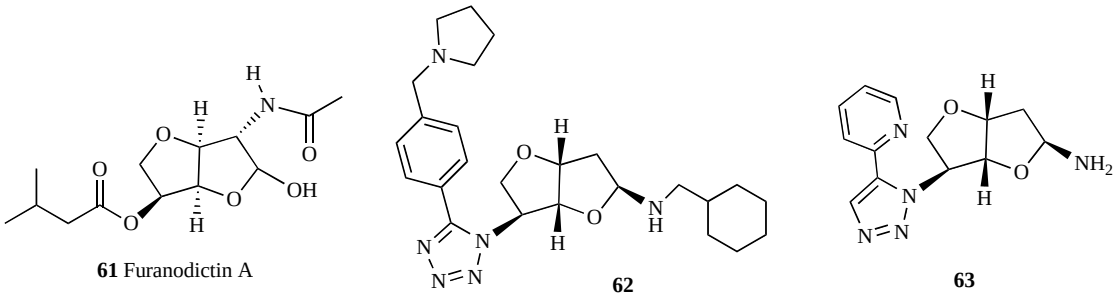


Fig. (3). Examples of phosphatase inhibitors with isomannide scaffold.

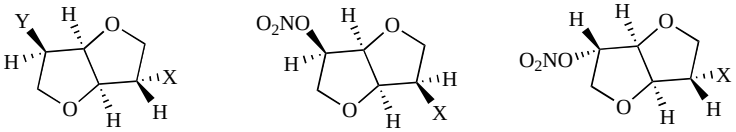


Fig. (4). Structures of isosorbide, isomannide and isoidide nitrates.

(Fig. **3**). The pharmacological screening of this series of isomannide-based inhibitors has shown potent inhibition of tyrosine phosphatases Shp-2 and PTP1B, e.g. compounds **62** and **63**. Shp-2 is commonly considered a target in the development of new anti-infectives, and inhibition of PTP1B is an actively pursued approach for the development of drugs against diabetes type II, obesity, and the metabolic syndrome [41].

Organic nitrates [42] as isosorbide dinitrate **64a** are currently used as therapeutics for cardiovascular disorders [43]. The pharmacology of **64a** and their isomers such as isomannide dinitrate **65a** have been extensively studied for the treatment of hypertension, angina pectoris and other ailments. Mononitrate derivatives **64b**, **64c**, **65b** and **66b** have been also reported providing structure-activity relationship studies (SAR) that showed activity to increase when the OH group maintained the same position as the NO_2 group. Isoidide mononitrate **66b** and isomannide mononitrate **65b**, with both the OH and NO_2 groups in the *exo* and *endo* positions, respectively, were the most active mononitrates (Fig. **4**) [44].

CONCLUSIONS

Isomannide, inexpensive and easily accessible building block, has attracted interest as starting material for a wide of synthetic reactions. Here we showed the different applications of Isomannide and derivatives in different areas such for polymer syntheses, asymmetric syntheses and, recently, in the synthesis of ionic liquids. Of particular importance is its use on the production of pharmaceutically important compounds. Isomannide itself is a kind of "U" shape structure so forcing a kind of beta-sheet structure in a given compound. Inversion of configuration on the hydroxy groups leads to a kind of "W" type structure so forcing a *quasi* linear structure. These easy structural manipulations are of great importance in designing new compounds, in particular peptide mimetic compounds.

ACKNOWLEDGEMENTS

The authors dedicate this manuscript in memory of Professor Octavio Augusto Ceva Antunes, his wife Patricia, and son Matheus, whose lives were lost in the Air France disaster on June 1, 2009.

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