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(54) **Title**: SYNTHESIS OF ISOHEXIDE ETHERS AND CARBONATES

(57) **Abstract**: A facile, straightforward method for alkylation of anhydrosugar alcohols (isohexides) using a carbonate reagent is described. The alkylation method involves: a) contacting in a solution of an isohexide with a dialkyl, diallyl, or diaryl carbonate, and the solution includes a Brnsted base; and b) producing either an alkyl ether or alkyl carbonate of the isohexide compound. The alkylation reaction is in situ, that is, performed without an extrinsic catalyst. According to the method, one can synthesize various ethers and carbonates.

SYNTHESIS OF ISOHEXIDE ETHERS AND CARBONATES

BENEFIT OF PRIORITY

The present application claims benefit of priority of U.S. Provisional Application No. 61/918,795, filed on December 20, 2013, the contents of which are incorporated herein by reference.

FIELD OF INVENTION

The present invention is in the field of art that relates to cyclic bi-functional materials useful as monomers in polymer synthesis and as intermediates generally, and to the methods by which such materials are made. In particular, the present invention pertains to a method of preparing anhydrosugar ethers and carbonates.

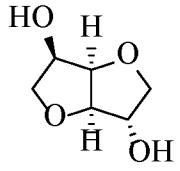
BACKGROUND

Traditionally, polymers and commodity chemicals have been prepared from petroleum-derived feedstock. As petroleum supplies have become increasingly costly and difficult to access, interest and research has increased to develop renewable or "green" alternative materials from biologically-derived sources for chemicals that will serve as commercially acceptable alternatives to conventional, petroleum-based or -derived counterparts, or for producing the same materials as produced from fossil, non-renewable sources.

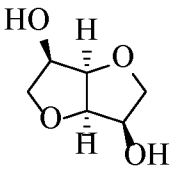
One of the most abundant kinds of biologically-derived or renewable alternative feedstock for such materials is carbohydrates. Carbohydrates, however, are generally unsuited to current high temperature industrial processes. Compared to petroleum-based, hydrophobic aliphatic or aromatic feedstocks with a low degree of functionalization, carbohydrates such as polysaccharides are complex, multi-functionalized hydrophilic materials. As a consequence, researchers have sought to produce biologically-based chemicals that can be derived from carbohydrates, but which are less highly functionalized, including more stable bi-functional compounds. One class of such compounds include anyhydrosugars, such as 1,4:3,6-dianhydrohexitols.

1,4:3,6-Dianhydrohexitols (also referred to herein as isohexides) are derived from renewable resources from cereal-based polysaccharides. Isohexides embody a class of bicyclic furanodiols that derive from the corresponding reduced sugar alcohols (D-sorbitol, D-mannitol, and D-iditol respectively). Depending on the chirality, three isomers of the isohexides exist, namely: A) isosorbide, B) isomannide, and C) isoidide, respectively; the structures of which are illustrated in Scheme 1.

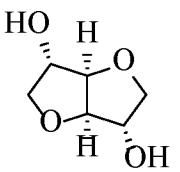
Scheme 1: A B C



isosorbide
from D-sorbitol



isomannide
from D-mannitol



isoidide
from D-iditol

These molecular entities have received considerable interest and are recognized as valuable, organic chemical scaffolds for a variety of reasons. Some beneficial attributes include relative facility of their preparation and purification, the inherent economy of the parent feedstocks used, owing not only to their renewable biomass origins, which affords great potential as surrogates for non-renewable petrochemicals, but perhaps most significantly the intrinsic chiral bi-functionalities that permit a virtually limitless expansion of derivatives to be designed and synthesized.

The isohexides are composed of two *cis*-fused tetrahydrofuran rings, nearly planar and V-shaped with a 120° angle between rings. The hydroxyl groups are situated at carbons 2 and 5 and positioned on either inside or outside the V-shaped molecule. They are designated, respectively, as *endo* or *exo*. Isoidide has two *exo* hydroxyl groups, while the hydroxyl groups are both *endo* in isomannide, and one *exo* and one *endo* hydroxyl group in isosorbide. The presence of the *exo* substituents increases the stability of the cycle to which it is attached. Also *exo* and *endo* groups exhibit different reactivities since they are more or less accessible depending on the steric requirements of the derivatizing reaction.

As interest in chemicals derived from natural resources is increases, potential industrial applications have generated interest in the production and use of isohexides. For instance, in the field of polymeric materials, the industrial applications have included use of these diols to synthesize or modify polycondensates. Their attractive features as monomers are linked to their rigidity, chirality, non-toxicity, and the fact that they are not derived from petroleum. For these reasons, the synthesis of high glass transition temperature polymers with good thermo-mechanical resistance and/or with special optical properties is possible. Also the innocuous character of the molecules opens the possibility of applications in packaging or medical devices. For instance, production of isosorbide at the industrial scale with a purity satisfying the requirements for polymer synthesis suggests that isosorbide can soon emerge in industrial polymer applications. (*See e.g.*, F. Fenouillot *et al.*, "Polymers From Renewable 1,4:3,6-Dianhydrohexitols (Isosorbide, Isommanide and Isoidide): A Review," PROGRESS IN POLYMER SCIENCE, vol. 35, pp.578-622 (2010); or X. Feng *et al.*, "Sugar-based Chemicals for Environmentally sustainable Applications," CONTEMPORARY SCIENCE OF POLYMERIC MATERIALS, Am. Chem. Society, Dec. 2010; or isosorbide-based plasticizers, e.g., U.S. Patent No. 6,395,810, contents of each are incorporated herein by reference.)

A kind of derivative that can be made is ethers of isohexides. Conventionally, ethers of dianhydrosugars are prepared by contacting alkyl halides and dialkylsulfates with an anhydrosugar, in

the presence of a base or phase transfer catalysts (PTC's, e.g., tetra-n-butylammonium bromide, benzyltriethyammonium bromide or N-methyl-N,N-dioctyloctan-1-aminium chloride). Notwithstanding the inherent costs of these exotic PTC's, these processes generally need highly pure anhydrosugar feedstock as a starting material, and suffer from both cumbrous and costly downsteam separation operations to effectuate propitious target purities. These issues have complicated efforts to achieve cost effective yields at significant quantity and quality.

To better take advantage of isohexides as a green feedstock, a clean and simple method of preparing the isohexides as a platform chemical or precursor that can be subsequently modified to synthesize other compounds would be welcome by those in the green or renewable chemicals industry. A more cost efficient process is needed as a way to unlock the potential of anhydrosugars and their derivative compounds, as these chemical entities have gained attention as valuable antecedents for the preparation of polymers, solvents, additives, lubricants, and plasticizers, etc. Furthermore, the inherent, immutable chirality of anhydrosugars makes these compounds useful as potential species for pharmaceutical applications or candidates in the emerging chiral auxiliary field of asymmetric organic synthesis. Given the potential uses, a cost efficient and simple process that can synthesis derivatives from anhydrosugars would be appreciated by manufacturers of both industrial and specialty chemicals alike as a way to better utilize biomass-derived carbon resources.

SUMMARY OF THE INVENTION

The present disclosure describes a method for alkylation of anhydrosugar alcohols (isohexides) using a carbonate reagent. In particular, the alkylation method involves: a) contacting an isohexide with a dialkyl, diallyl, or diaryl carbonate, and a Brønsted base; and b) producing at least an alkyl ether or alkyl carbonate of the isohexide compound. The alkylation reaction is *in situ*, that is, performed without an extrinsic catalyst. The Brønsted base has a pKa of at least 4, which helps deprotonates the isohexide compound. The isohexide is at least one of the following: isosorbide, isomannide, and isoidide. The dialkyl, diallyl, or diaryl carbonate has an R-group having 1 to 20 carbon atoms. When the R-group is at least a methyl, ethyl, propyl group, an ether is produced, and when the R-group is at least a C_4-C_{20} group, a carbonate is generated. The resultant ether or carbonate, respectively, can be either: a mono-alkyl ether or dialkyl ether, or mono-alkyl, mono-allyl, mono-aryl carbonate, or dialkyl, diallyl, or diaryl carbonate.

In another aspect, the present disclosure pertains to certain ethers and carbonates synthesized according the foregoing method. In general, the alkylated ether of the isohexide compound is at least one of the following: mono-ether of isoidide; mono-ether of isomannide; mono-ether of isosorbide; di-ether of isoidide; di-ether of isomannide; and di-ether of isosorbide, wherein the resultant ether has at least one of the following alkyl groups: a mono-methyl, mono-ethyl, mono-propyl, di-methyl, di-ethyl, or di-propyl. Generally, the alkylated carbonate of the isohexide compound is at least one of the following: mono-carbonate of isoidide; mono-carbonate of isomannide; mono-carbonate of

isosorbide; di-carbonate of isoidide; di-carbonate of isomannide; and di-carbonate of isosorbide, wherein the resultant carbonate has at least one of the following alkyl, allyl or aryl groups: a mono-butyl, mono-pentyl, mono-hexyl, mono-benzyl, mono-phenyl, mono-allyl, di-butyl, di-pentyl, dihexyl, di-benzyl, di-phenyl, di-allyl, or a mono- or di-alkyl group from C_7-C_{20} carbon atoms.

Additional features and advantages of the present process will be disclosed in the following detailed description. It is understood that both the foregoing summary and the following detailed description and examples are merely representative of the invention, and are intended to provide an overview for understanding the invention as claimed.

DETAILED DESCRIPTION OF THE INVENTION

Section I. – Description

As biomass derived compounds that afford great potential as surrogates for non-renewable petrochemicals, 1,4:3,6-dianhydrohexitols are a class of bicyclic furanodiols that are valued as renewable molecular entities. (For sake of convenience, 1,4:3,6-dianhydrohexitols will be referred to as "isohexides" in the Description hereinafter.) As referred to above, the isohexides are good chemical platforms that have recently received interest because of their intrinsic chiral bi-functionalities, which can permit a significant expansion of both existing and new derivative compounds that can be synthesized.

Isohexide starting materials can be obtained by known methods of making respectively isosorbide, isomannide, or isoidide. Isosorbide and isomannide can be derived from the dehydration of the corresponding sugar alcohols, D-sorbitol and D mannitol respectively. As a commercial product, isosorbide is also available easily from a manufacturer. The third isomer, isoidide, can be produced from L-idose, which rarely exists in nature and cannot be extracted from vegetal biomass. For this reason, researchers have been actively exploring different synthesis methodologies for isoidide. For example, the isoidide starting material can be prepared by epimerization from isosorbide. In L. W. Wright, J. D. Brandner, *J. Org. Chem.*, 1964, *29* (10), pp. 2979–2982, epimerization is induced by means of Ni catalysis, using nickel supported on diatomaceous earth. The reaction is conducted under relatively severe conditions, such as a temperature of 220°C to 240°C at a pressure of 150 atmospheres. The reaction reaches a steady state after about two hours, with an equilibrium mixture containing isoidide (57-60%), isosorbide (30-36%) and isomannide (5-7-8%). Comparable results were obtained when starting from isoidide or isomannide. Increasing the pH to 10-11 was found to have an accelerating effect, as well as increasing the temperature and nickel catalyst concentration. A similar disclosure can be found in U.S. Patent No. 3,023,223, which proposes to isomerize isosorbide or isomannide. More recently, P. Fuertes proposed a method for obtaining L-iditol (precursor for isoidide), by chromatographic fractionation of mixtures of L-iditol and L-sorbose (U.S. Patent Publication No. 2006/0096588; U.S. Patent No. 7,674,381 B2). L-iditol is prepared starting from sorbitol. In a first step sorbitol is converted by fermentation into L-sorbose,

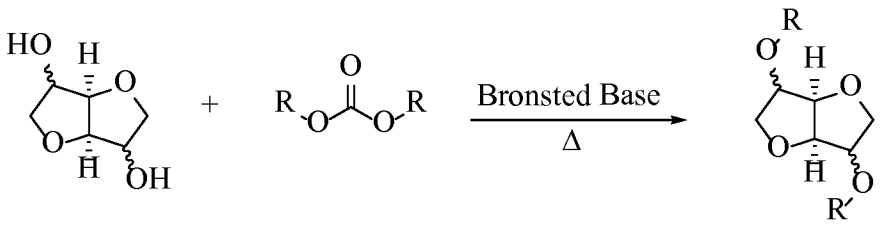
which is subsequently hydrogenated into a mixture of D-sorbitol and L-iditol. This mixture is then converted into a mixture of L-iditol and L-sorbose. After separation from the L-sorbose, the L-iditol can be converted into isoidide. Thus, sorbitol is converted into isoidide in a four-step reaction, in a yield of about 50%. (The contents of the cited references are incorporated herein by reference.)

These molecular entities hold significant potential as "green", renewable solvents derived from biomass, as well as platform chemicals (monomethyl ethers) for the production of surfactants, dispersants, and emollients (personal care products). Furthermore, the reagents used in the aforementioned preparation are non-toxic, environmentally friendly substances.

A.

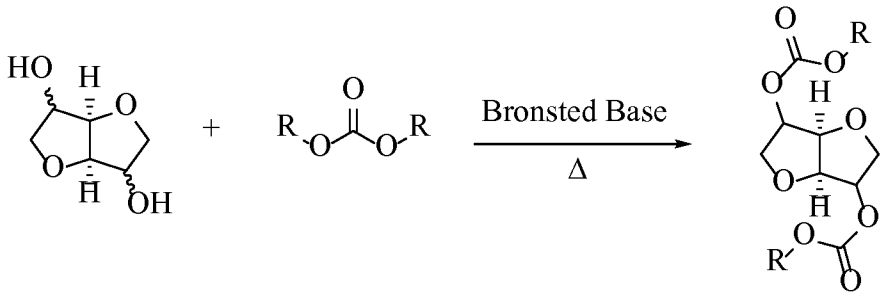
In the present disclosure, benign, environmentally friendly carbonate (e.g., diethyl carbonate or potassium carbonate) are employed to synthesize ethers and carbonates. Schemes 1 and 2 are generalized illustrations of embodiments of the present synthesis process. Scheme 1 depicts an embodiment in which an isohexide is reacted with a carbonate having C_1-C_3 alkyl R-groups using a Brønsted base to generate a corresponding ether. Scheme 2 shows an alternate embodiment in which an isohexide is reacted with a carbonate having C_4 and greater alkyl, phenyl, allyl R-groups using a Brønsted base to produce a corresponding carbonate. The base serves to deprotontate the isohexide intermediate to generate the ether or carbonate compounds. The base should be reasonably soluble in solution to afford satisfactory mixing and subsequent reactivity.

Scheme 1. Ethers



Bronsted base = carbonates, hydroxides, amines, hydrides
R = C1-C3 alkyl groups

Scheme 2. Carbonates



Bronsted base = carbonates, hydroxides, amines, hydrides

R = C4 and higher alkyl, phenyl, allyl

Preferably, the reaction time for each synthesis can be within about 24 hours. Typically, the reaction time is within about 6 hours to about 12 hours (e.g., 7 or 8 hours to about 9 or 10 hours). As the reaction proceeds for longer durations (e.g., ~10-24 hours) the yields respectively of mono-ether and di-ether products will increase to full conversion of the di-ether species. For the carbonate products, the mono-carbonate species quickly converts to the di-carbonate species within about 1-2 hours.

The Brønsted base should have a minimal pKa of about 4 (e.g., pyridine). Typically, the base pKa is about 7-14, usually about 8 or 10 to about 12 or 13. In alternative embodiments, some bases may have a greater pKa, up to about 40-55 (e.g., alkyl-lithium). Various kinds of Brønsted bases can be used, for example, the base can be one of the following: a carbonate (e.g., sodium or potassium carbonate); a hindered amine (e.g., triethylamine, tributylamine, diisopropylethylamine (DIEA), dibutylamine); a nucleophilic base (e.g., pyridine, pyrimidine, dimethyl-aminopyridine, imidazole, pyrrolidine, morpholine); a sodium, potassium, or calcium hydride; or an organometallic compound (e.g., alkyl-lithium or alkyl-magnesium). The minimum stoichiometric equivalents of base to the staring materials is about 1 for mono-ether or mono-carbonate, and about 2 equivalents depending on the solubility of the carbonate or miscibility of the base (e.g., amines) in solution.

Using a non-nucleophilic amine that is sterically hindered, such as diisopropylethylamine (DIEA), can enhance the process not only from its solubilizing capacity and basicity, but ease of sequestration via mild aqueous acid treatment.

The Brønsted base in some embodiments is a solid compound, such as a mineral carbonate, which would make the removal and purification of the final product from solution easier. In other embodiments, hindered amines, owing to their innate liquidity and ease of segregation by mild acid treatment comprise other salutary bases for this process. The liquid hindered amine allows for better mixing and miscibility but removal is more complex involving a titration with acid and then liquid-liquid extraction.

For instance, isosorbide diallyldicarbonate separates in the form of viscous oil, and can be stored indefinitely, with negligible degradation, in an inert atmosphere.

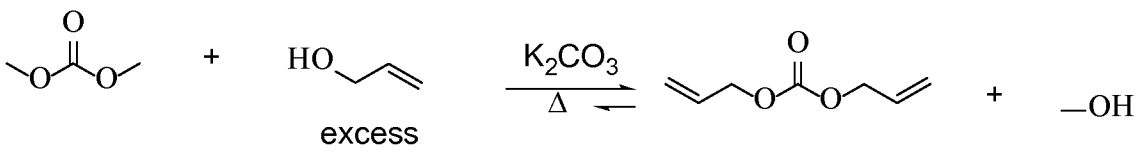
According to the present invention, the alkylation reaction can be conducted at a temperature in a range from about 70°C or 80°C to about 180°C or 200°C, inclusive, depending on the boiling point temperature of the particular carbonate solvent used in the reaction (e.g., 75°C for dimethyl carbonate, or 120°C for diethyl carbonate). Typically, the reaction temperature is in a range from about 85°C or 90°C or 100°C to about 160°C, 170°C or 175°C, inclusive of various combinations of ranges therein. As a general consideration, the longer or greater the number of carbons in an alkyl, allyl or aryl group, respectively, of the dialkyl, diallyl, or diaryl carbonate reagent, the higher the boiling point tends to be; hence, the greater the reaction temperature. As a precaution, one risks decarboxylation of the carbonate even though one may achieve greater conversion of the isohexide to its corresponding ether or carbonate at significantly higher temperatures. Particular temperature ranges for example may be from about 110°C or 120°C to about 140°C or 150°C, inclusive of combination of ranges therein. In certain desirable iterations, the reaction is performed at a temperature between about 115°C, 117°C or 120°C to about 125°C, or 130°C, or 135°C.

To prepare monoethers, the reaction should use at least 1 to 2 equivalents of carbonate for each equivalent of isohexide consumed. For diethers, at least 2 equivalents are used.

We observe that carbonates with R-groups having C_1-C_3 carbons tend to generate ethers, while those with C_4-C_6 make predominately carbonates, and those with C_7-C_{20} make only carbonates. It is believed that the possible steric interference from longer chain alkyl, allyl, or aryl groups tends to favor the formation of the carbonate species over the ether species.

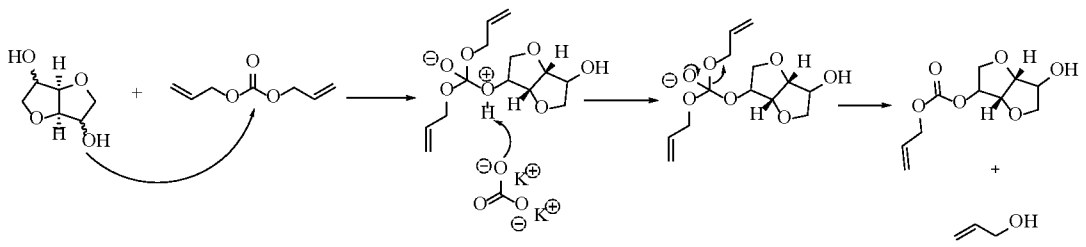
Typically as a solvent, one may include an alcohol having the same R-species as that which is displaced from the carbonate molecule, such as, an ethanol when reacting with diethylcarbonate, or an allyl alcohol when using diallylcarbonate, such in Scheme 3. It is believed that in surplus alcohol the carbonate is activated.

Scheme 3.



In situ transesterification of the incumbent carbonate with excess alcoholic solvent occurs readily, auspiciously permitting alkyl etherification to occur without the need for use of carbonates other than inexpensive dimethylcarbonate. This is shown in Scheme 4.

Scheme 4. Transesterification of the isohexide and carbonate removes the allyl alcohol



The reactions can be executed in a neat solution of dimethyl or ethylcarbonate, or as previously detailed, can be generated *in situ* via transesterification. The isohexide compound and the dialkyl, diallyl, or diaryl carbonate are reacted respectively in a neat solution of at least the dialkyl, diallyl, or diaryl carbonate. As a cost efficient feature, one can recycle the unconsumed dicarbonate and solvent.

Given the difference in boiling points of the carbonate (~95°C) and amine (~120°C), the present etherification reactions can simplify and make the purification and recovery process relatively easy. One can distill both the carbonate and the amine and recycle recovered carbonate after each reaction.

An illustration of an advantage of the present synthesis process is the employment of relatively mild conditions and safe non-toxic reagents is, for example, the preparation of (3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl diphenyl dicarbonate, isosorbide diphenylcarbonate, as discussed in Example 4, below. In contrast, the conventionally way of preparing the same compound can involve several reaction steps, and uses harsh conditions and some reagents such as diphosgene or triphosgene, which are toxic (see, e.g., Noordover, Bart A.J., *et al.*, "Chemistry, Functionality, and Coating Performance of Biobased Copolycarbonates from 1,4:3,6-Dianhydrohexitols," J. APPLIED POLYMER SCIENCE, Vol. 121, 1450-1463 (2011); Sun, S. J., *et al.*, "New polymers of carbonic acid. XXV. Photoreactive cholesteric polycarbonates derived from 2,5-bis(4′-hydroxybenzylidene)cyclopentanone and isosorbide" J. POLYMER SCIENCE: PART A: POLYM. CHEM., Vol. 37, 1125-1133 (1999); Kricheldorf, H.R., *et al.*, "Polymers of Carbonic Acid," MACROMOLECULES, Vol. 29, 8077-8082 (1996)).

B.

Several plausible variations to the present synthesis methodology can be applied to generate high yields of monoethyl or diethyl targets. These adjustments may include, though are not restricted to:

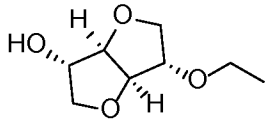
1) organic bases: all linear and cyclic amines, such as triethylamine, Hunig's base, DBU, and piperidine;

2) inorganic bases: alkali and alkali earth metal carbonates, such as cesium carbonate, calcium carbonate;

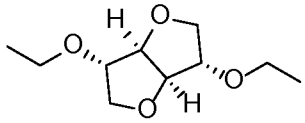
3) basic resins: for continuous processes, resins with basic-capped functionalities;

4) other alkyl carbonates: transesterification of carbonates that can be implimented with relatively inexpensive dimethyl or diethyl carbonates in an excess alcohol and with a Lewis acid catalyst. For example, isoidide mono and dibenzylethers can be generated from the *in situ* production of dibenzyl carbonate (dimethyl carbonate, a surfeit of benzyl alcohol, and catalyst) using the present method.

The alkylated isohexide compound prepared by the present method is either an ether or a carbonate. The isohexide ether can be at least one of the following: a mono-alkyl ether or dialkyl ether. The ether compound can be, for example: an isoidide monoethylether, with a structure:



; or an isoidide diethylether, with a structure:



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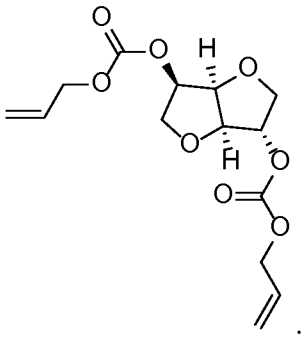
In other embodiments, the alkylated isohexide ether can be one of the following: mono-methyl ether of isoiodide; mono-ethyl ethers, of isosorbide, isommanide, or isoiodide, respectively; diethyl ester of isoiodide; mono-propyl ether of isomannide; dipropyl ether of isomannide; mono-propyl ether of isoidide; dipropyl ether of isoiodide; mono-benzyl ether of isoidide; monoallyl ethers of isosorbide, isommanide, or isoiodide, respectively; and diallyl ethers of isosorbide, isommanide, or isoiodide, respectively.

Isoidide monoethylether (IUPAC: (3S,3aR,6S,6aR)-6-ethoxyhexahydrofuro[3,2-b]furan-3-ol) and isoidide diethylether (IUPAC: (3S,3aR,6S,6aR)-6-ethoxyhexahydrofuro[3,2-b]furan-3-ol). Examples of the diethyl ethers of isomannide and isosorbide, as well as the corresponding monoethyl ethers can be formed in high yields. It is believed that the monomethyl ethers of isomannide and isosorbide are new compositions of matter.

When a carbonate is made according to the present method, the carbonate compound can be at least one of the following: a mono-alkyl carbonate, dialkyl carbonate, mono-or di-aryl carbonate, mono- or di-allyl carbonate, or a carbonate with an alkyl group from 4-20 carbon atoms. In an example, the carbonate compound is: isosorbide diallyldicarbonate, with a structure:



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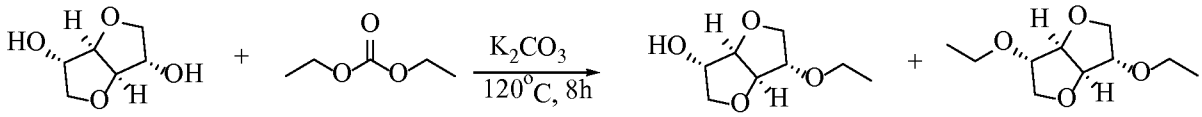
In other embodiments, the isohexide carbonate can be one of the following: mono-methylcarbonate of isomannide; mono-methylcarbonate of isoidide; dimethylcarbonate of isomannide; dimethylcarbonate of isoidide; monoethylcarbonates of isosorbide, isommanide, or isoiodide, respectively; diethylcarbonate of isomannide; diethylcarbonate of isoidide; mono-propyl or dipropylcarbonates of isosorbide, isommanide, or isoiodide, respectively; mono- or dicarbonates having an alkyl R-group of C_4 to C_{20} of isosorbide, isommanide, or isoiodide, respectively; mono-benzyl or dibenzyl carbonates of isosorbide, isommanide, or isoiodide, respectively; monophenylcarbonates of isosorbide, isommanide, or isoiodide, respectively; and diphenylcarbonates of isomannide or isoidide, respectively.

Particular illustrative examples of derivative compounds that can be made from both FDM and THF-sulfonates are presented in the associated examples that follow.

Section II. – Examples

The following examples are provided as illustration of the different aspects of the present disclosure, with the recognition that altering parameters and conditions, for example by change of temperature, time and reagent amounts, and particular starting species and catalysts and amounts thereof, can affect and extend the full practice of the invention beyond the limits of the examples presented.

Example 1: Ethyl etherification of isoidide with diethyl carbonate and potassium carbonate



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Experimental: A 100 mL boiling flask equipped with a PTFE coated magnetic stir bar was charged with 2 grams of isoidide (13.7 mmol), 9.45 grams of potassium carbonate (68.4 mmol), and 50 mL of diethyl carbonate (413 mmol). While stirring, the heterogeneous mixture was heated to 120°C for 8 hours. After this time, the residual potassium carbonate was removed by filtration, the filtrate stored. Three spots were identified on TLC (98% EtOAc/2% MeOH, cerium molybdate stain), $Rf_1 = 0.76$, $Rf_2 = 0.44$, $Rf_3 = 0.24$ (isoidide). A sample was analyzed, qualitatively, by GC/MS that revealed a very small amount of residual isoidide, with two preponderant signals that were congruous with the mono and diethyl analogs of isoidide. A sample was then submitted for quantitative analysis, which produced the following mass ratios: Isoidide - 12.5%; isoidide monoethyl ether - 50.9%; isoidide diethyl ether - 33.7%.

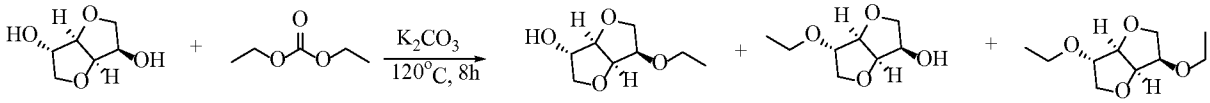
Comparative Example 1: Failed etherification of isoidide with diethyl carbonate, potassium carbonate, and ethanol.

A 100 mL boiling flask was charged with 2 grams of isoidide (13.7 mmol), 9.45 grams of potassium carbonate (68.4 mmol), 8.30 mL of diethyl carbonate (68.4 mmol) and 50 mL of ethanol. The heterogeneous mixture was heated to reflux (~85°C for 24 hours. Samples of the reaction mixture were removed at 2 hour increments and analyzed by GC/MS. After 24 h, no mono or di-methyl ethers of isoidide were descried.

It is interesting that isoidide methyl etherification was quantitative with dimethylcarbonate in methanol but completely failed with diethyl carbonate in ethanol. An explicit rationalization cannot be

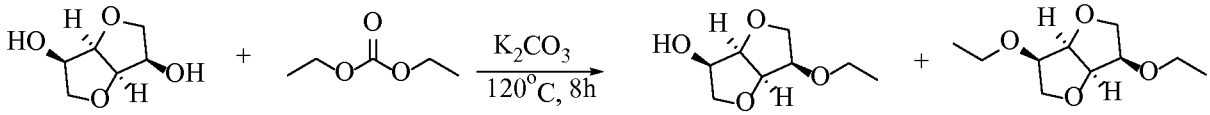
derived at this time, but could involve either 1) steric effects of the ethyl chain and/or 2) solubility of potassium carbonate in ethanol.

Example 2: Ethyl etherification of isosorbide with diethyl carbonate and potassium carbonate.



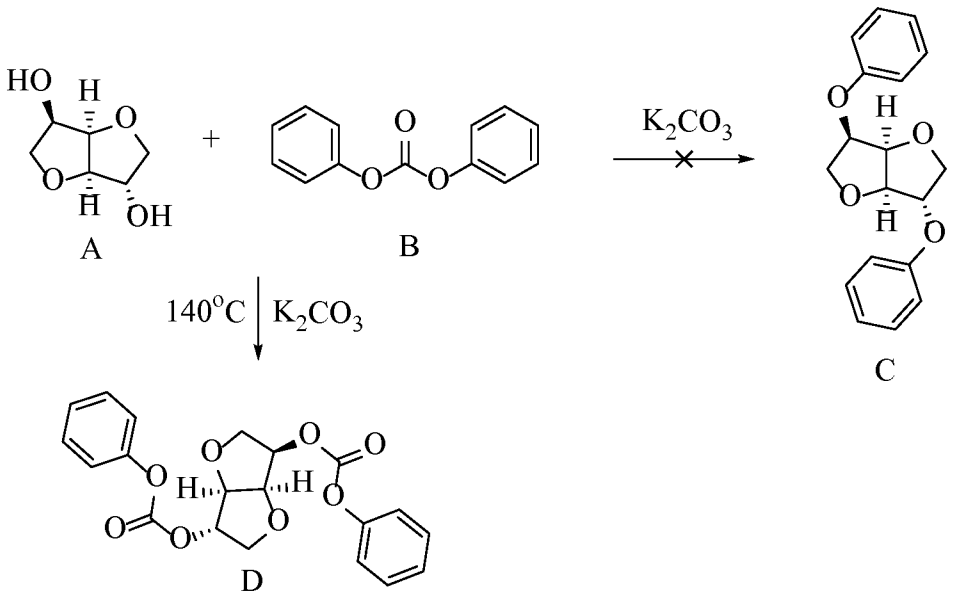
Experimental: A 100 mL boiling flask equipped with a PTFE coated magnetic stir bar was charged with 2 grams of isosorbide (13.7 mmol), 9.45 grams of potassium carbonate (68.4 mmol), and 50 mL of diethyl carbonate (413 mmol). While stirring, the heterogeneous mixture was heated to 120°C for 8 hours. After this time, the residual potassium carbonate was removed by filtration, the filtrate stored. Four spots were identified on TLC (98% EtOAc/2% MeOH, cerium molybdate stain), $Rf_1 = 0.76$, $Rf_2 = 0.44$, $Rf_3 = 0.42$ and $Rf_4 = 0.20$ (isosorbide). A sample was analyzed, qualitatively, by GC/MS that revealed a very small amount of residual isosorbide, with three primary signals that were consistent with the mono and diethyl analogs of isoidide. A sample was then submitted for quantitative analysis, which produced the following mass ratios: Isosorbide - 15.2%; isosorbide monoethyl ethers - 55.2%; isosorbide diethyl ether - 26.7%.

Example 3: Ethyl etherification of isomannide with diethyl carbonate and potassium carbonate.



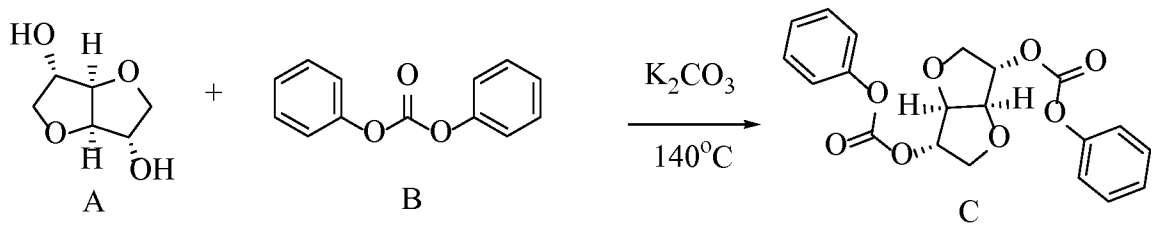
Experimental: A 100 mL boiling flask equipped with a PTFE coated magnetic stir bar was charged with 2 grams of isomannide (13.7 mmol), 9.45 grams of potassium carbonate (68.4 mmol), and 50 mL of diethyl carbonate (413 mmol). While stirring, the heterogeneous mixture was heated to 120°C for 8 hours. After this time, the residual potassium carbonate was removed by filtration, the filtrate stored. Three spots were identified on TLC (98% EtOAc/2% MeOH, cerium molybdate stain), $Rf_1 = 0.78$, $Rf_2 = 0.39$, and $Rf_3 = 0.18$ (isomannide). A sample was analyzed, qualitatively, by GC/MS that revealed a very small amount of residual isomannide, with two primary signals that were consistent with the mono and diethyl analogs of isomannide. A sample was then submitted for quantitative analysis, which produced the following mass ratios: Isomannide -13.1%; isosorbide monoethyl ethers - 49.4%; isosorbide diethyl ether - 30.5%.

Example 4: Synthesis of (3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl diphenyl dicarbonate, Isosorbide Diphenylcarbonate, **D**



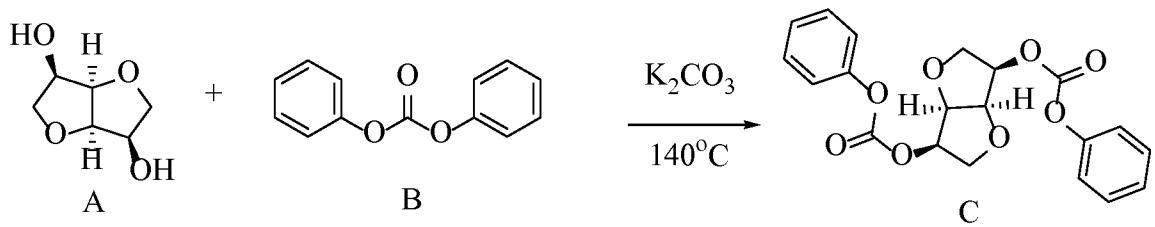
Experimental: A 25 mL round bottomed flask equipped with an oval PTFE coated magnetic stir bar was charged with 1 g of isosorbide **A** (6.84 mmol), 3.78 g of potassium carbonate (27.36 mmol) and 10 g of diphenylcarbonate **B** (46.7 mmol). While stirring, the heterogeneous mixture was heated to 140°C overnight (a profusion of effervescence was noted). At this time the reaction was deemed complete by TLC (1% methanol in ethyl acetate, UV-Vis and cerium molybdate illumination) as signified by the absence of isosorbide and presence of only 2 spots. The heterogeneous mixture was diluted with ethanol and filtered to remove excess salts. A white solid appeared in the filtrate during the sequestration, which was filtered, dried, and analyzed by ^{1}H NMR, indicating isosorbide diphenylcarbonate **D** (1.55 g, 59%). No isosorbide diphenylether **C** was descried by this analytical technique in the mother liquor. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.41-7.40 (m, 4H), 7.39-7.38 (m, 4H), 7.22-7.20 (m, 2H), 5.24-5.21 (m, 1H), 5.03 (d, J = 5.6 Hz, 1H), 4.67 (t, J = 9.8 Hz, 1H), 4.33 (d, J = 8.2 Hz, 1H), 4.26 (d, J = 10.4 Hz, 1H), 4.23-4.22 (dd, J = 9.8 Hz, J = 1.4 Hz, 1H), 4.15-4.14 (dd, J = 9.6 Hz, J = 3.2 Hz, 1H), 4.02-4.01 (dd, J = 9.2 Hz, J = 2.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 153.32, 153.01, 151.26, 151.10, 129.88, 129.81, 121.31, 115.55, 86.04, 82.00, 81.31,76.94, 73.44, 70.90.

Example 5. Synthesis of (3S,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl diphenyl dicarbonate, **C**



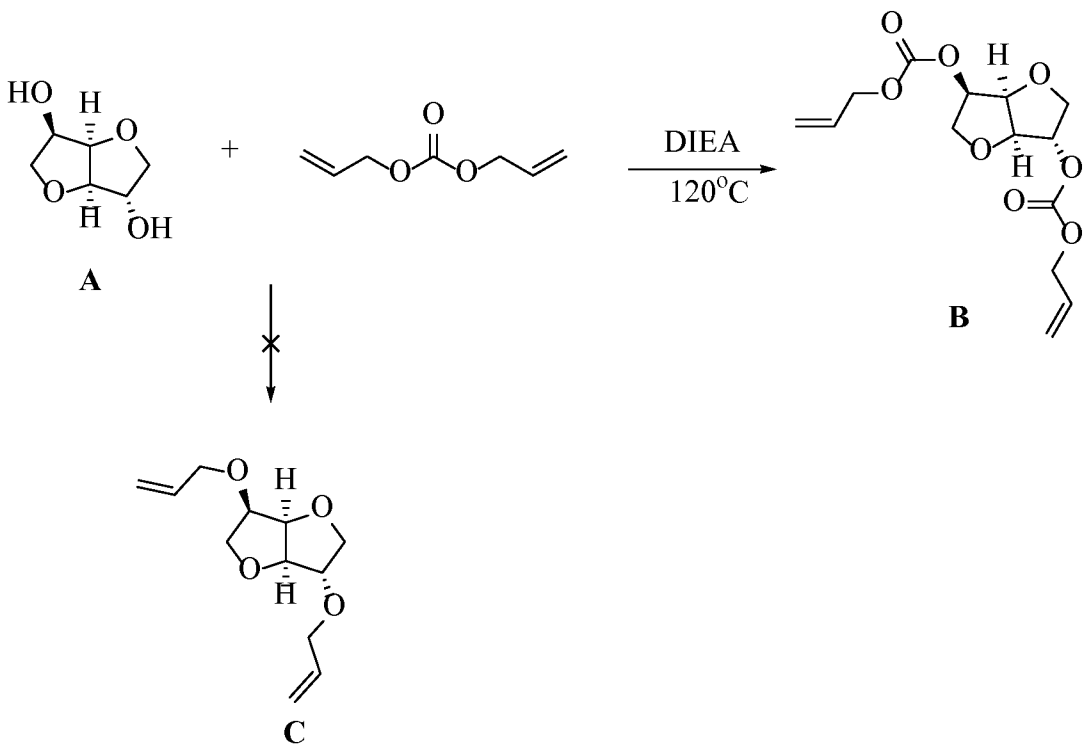
Experimental: A 25 mL round bottomed flask equipped with an oval PTFE coated magnetic stir bar was charged with 1 g of isoidide **A** (6.84 mmol), 3.78 g of potassium carbonate (27.36 mmol) and 10 g of diphenylcarbonate **B** (46.7 mmol). While stirring, the heterogeneous mixture was heated at 140°C overnight (significant bubbling was observed). After this time the reaction was deemed complete by TLC (1% methanol in ethyl acetate, UV-Vis and cerium molybdate illumination) as signified by the absence of isoidide and presence of only 2 spots. The heterogeneous mixture was diluted with ethanol and filtered to remove excess salts. A white solid appeared in the filtrate during the sequestration, which was filtered, dried, and analyzed by ^{1}H NMR, indicating isoidide diphenylcarbonate **D** (1.76 g, 66%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.36-7.34 (m, 4H), 7.31-7.28 (m, 4H), 7.21-7.19 (m, 2H), 4.97-4.95 (m, 2H), 4.82 (d, J = 5.5 Hz, 4H), 4.37 (m, 2H), 4.32 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 153.67, 151.04, 129.92, 129.87, 122.07, 116.38, 89.52, 84.84, ,70.48.

Example 6: Synthesis of (3R,3aR,6R,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl diphenyl dicarbonate, C.



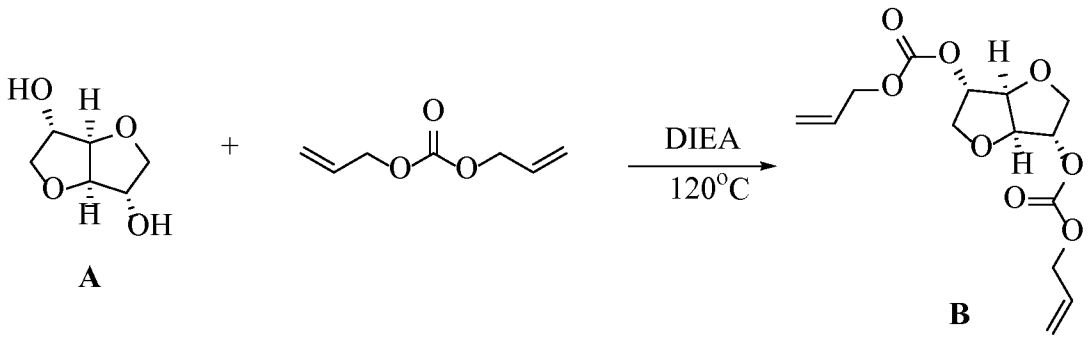
Experimental: A 25 mL round bottomed flask equipped with an oval PTFE coated magnetic stir bar was charged with 1 g of isomannide **A** (6.84 mmol), 3.78 g of potassium carbonate (27.36 mmol) and 10 g of diphenylcarbonate **B** (46.7 mmol). While stirring, the heterogeneous mixture was heated at 140°C overnight (significant bubbling was observed). After this time the reaction was deemed complete by TLC (1% methanol in ethyl acetate, UV-Vis and cerium molybdate illumination) as signified by the absence of isomannide and presence of only 2 spots. The heterogeneous mixture was diluted with ethanol and filtered to remove excess salts. A white solid appeared in the filtrate during the sequestration, which was filtered, dried, and analyzed by ^{1}H NMR, indicating isoidide diphenylcarbonate **D** (1.31 g, 49%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 7.41-7.40 (m, 4H), 7.39-7.38 (m, 4H), 7.22-7.20 (m, 2H), 5.12-5.09 (m, 2H), 4.97 (d, J = 5.8 Hz, 4H), 4.51 (m, 2H), 4.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 153.44, 150.94, 129.81, 129.77, 122.00, 116.03, 91.37, 86.38,70.23.

Example 7. Synthesis of diallyl((3R, 3aR, 6S, 6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)dicarbonate, isosorbide diallyldicarbonate



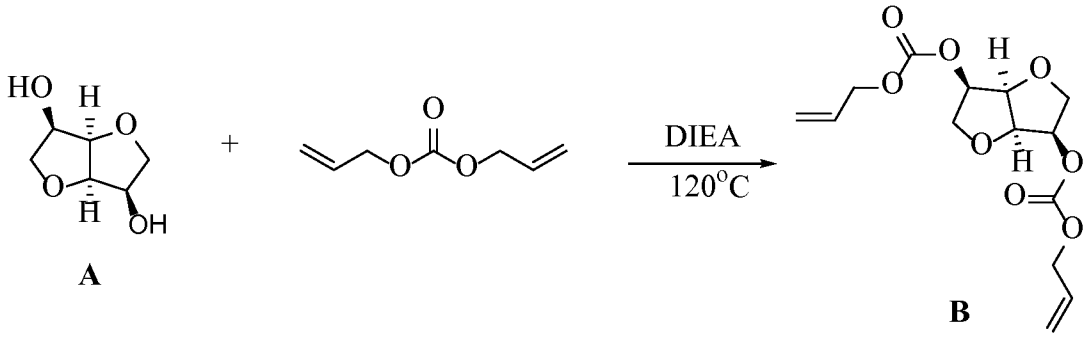
Experimental: An oven dried, 25 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 100 mg of isosorbide (**A**, 0.684 mmol), 1 mL of diallylcarbonate (7.03 mmol), and 477 µL of diisopropylethylamine (DIEA, 2.74 mmol). A reflux condenser capped with an argon inlet was affixed to the round bottomed flask and the mixture heated to 120°C overnight with vigorous stirring. After this time, an aliquot was removed, diluted with acetone and analyzed by GC/MS. The characteristic signal for isosorbide was absent, indicating full conversion. No other signals were manifest, precluding the presence of diallyisosorbide, **C** or monoallylisosorbide isomers. The absence of the diallyl analog was corroborated by TLC (1:1 EtOAc:Hexanes, cerium molybdate stain), where an authentic sample of diallylisosorbide was loaded adjacent to the product mixture. The signature spot was not observed in the product mixture. Product workup entailed dilution with acetone, filtration to remove orange solids, and concentration *in vacuo*, resulting in an oil with a light-yellow color (162 mg, 75.0%). ^{1}H NMR analysis ($CDCl_3$, 400 MHz) δ (ppm) 5.97-5.91 (m, 2H), 5.39-5.38 (dd, J = 13.2 Hz, J = 1.2 Hz, 1H), 5.35-5.34 (dd, J = 13.2 Hz, J = 1.3 Hz, 1H), 5.30-5.29 (dd, J = 8.6 Hz, J = 1.0 Hz, 1H), 5.27-5.26 (dd, J = 8.4 Hz, J = 1.2 Hz, 1H), 5.11-5.09 (m, 2H), 4.90 (t, J = 5.2 Hz, 1H), 4.67 (d, J = 6.4 Hz, 2H), 4.64 (d, J = 6.2 Hz), 4.57 (d, J = 6.6 Hz, 1H), 4.07-4.03, (m, 2H), 3.91-3.90 (m, 2H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 154.56, 154.21, 131.48, 131.34, 119.62, 119.28, 86.07, 81.43, 81.10, 73.46, 70.70, 69.07, 69.04, 68.89.

Example 8: Synthesis of diallyl ((3S,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl) dicarbonate, **B**.



Experimental: An oven dried, 25 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 100 mg of isoidide (**A**, 0.684 mmol), 1 mL of diallylcarbonate (7.03 mmol), and 477 µL of diisopropylethylamine (DIEA, 2.74 mmol). A reflux condenser capped with an argon inlet was affixed to the round bottomed flask and the mixture heated to 120°C overnight while vigorously stirring. After this time, an aliquot was removed, diluted with acetone and analyzed by GC/MS. The characteristic signal for isoidide was absent, indicating full conversion. Product workup entailed dilution with acetone, filtration to remove brown solids, and concentration *in vacuo*, resulting in an oil with a light-yellow color (144 mg, 66.9%). ^{1}H NMR analysis ($CDCl_3$, 400 MHz) δ (ppm) 5.97-5.91 (m, 2H), 5.49-5.46 (m, 2H), 5.35-5.34 (m, 2H), 4.97-4.95 (m, 2H), 4.80 (d, J = 5.5 Hz, 4H), 4.65 (d, J = 7.2 Hz, 4H), 4.35 (m, 2H), 4.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 153.33, 131.28, 117.74, 90.34, 81.63, 70.07, 62.51.

Example 9: Synthesis of diallyl ((3R,3aR,6R,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl) dicarbonate, **B**.



Experimental: An oven dried, 25 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 100 mg of isomannide (**A**, 0.684 mmol), 1 mL of diallylcarbonate (7.03 mmol), and 477 µL of diisopropylethylamine (DIEA, 2.74 mmol). A reflux condenser capped with an argon inlet was affixed to the round bottomed flask and the mixture heated to 120°C overnight with vigorous stirring. After this time, an aliquot was removed, diluted with acetone and analyzed by GC/MS. The characteristic signal for isomannide was absent, indicating full conversion. Product workup entailed dilution with acetone, filtration to remove brown solids, and concentration *in vacuo*, resulting in an oil with a light-yellow color (145 mg, 67.3%). ^{1}H NMR analysis ($CDCl_3$, 400 MHz) δ

(ppm) 5.95-5.90 (m, 2H), 5.46-5.44 (m, 2H), 5.33-5.31 (m, 2H), 5.11-5.08 (m, 2H), 4.96 (d, J = 5.8 Hz, 4H), 4.61 (d, J = 7.2 Hz, 4H), 4.53 (m, 2H), 4.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm) 153.72, 131.94, 117.38, 91.66, 82.07, 69.41, 60.99.

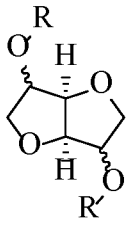
The present invention has been described in general and in detail by way of examples. Persons of skill in the art understand that the invention is not limited necessarily to the embodiments specifically disclosed, but that modifications and variations may be made without departing from the scope of the invention as defined by the following claims or their equivalents, including other equivalent components presently know or to be developed, which may be used within the scope of the invention. Therefore, unless changes otherwise depart from the scope of the invention, the changes should be construed as being included herein.

CLAIMS

We Claim:

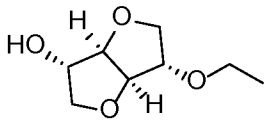
1. A method of alkylating an anhydrosugar compound comprising: a) contacting an isohexide compound with a dialkyl, diallyl, or diaryl carbonate and a Brønsted base; and b) producing at least an alkyl ether or alkyl carbonate of the isohexide compound.
2. The method according to claim 1, wherein the anhydrosugar compound is at least one of: isosorbide, isomannide, and isoidide.
3. The method according to claim 1, wherein said dialkyl, diallyl, or diaryl carbonate has an R-group having 1 to 20 carbon atoms.
4. The method according to claim 3, wherein when said R-group is at least one of methyl, ethyl, propyl group, said alkyl ether is produced predominantly.
5. The method according to claim 3, wherein when said R-group is at least a C_4-C_{20} group, said alkyl carbonate is produced predominantly.
6. The method according to claim 1, wherein said alkylated ether of said isohexide compound is at least one of: mono-ether of isoidide, mono-ether of isomannide, mono-ether of isosorbide, di-ether of isoidide, di-ether of isomannide, and di-ether of isosorbide.
7. The method according to claim 3, wherein said alkylated isohexide compound is an ether having at least one of the following alkyl groups: a mono-methyl, mono-ethyl, mono-propyl, di-methyl, di-ethyl, or di-propyl isohexide ether.
8. The method according to claim 1, wherein said alkylated carbonate of said isohexide compound is at least one of: mono-carbonate of isoidide; mono-carbonate of isomannide; mono-carbonate of isosorbide; di-carbonate of isoidide; di-carbonate of isomannide; and di-carbonate of isosorbide.
9. The method according to claim 5, wherein said alkylated isohexide compound is a carbonate having at least one of the following alkyl, allyl or aryl groups: a mono-butyl, mono-pentyl, mono-hexyl, mono-benzyl, mono-phenyl, mono-allyl, di-butyl, di-pentyl, dihexyl, di-benzyl, di-phenyl, di-allyl, or a mono- or di-alkyl group from C_7-C_{20} carbon atoms.
10. The method according to claim 1, wherein said anhydrosugar compound and said dialkyl, diallyl, or diaryl carbonate are contacted at a temperature in a range from about 70°C to about 200°C.
11. The method according to claim 10, wherein said anhydrosugar compound and said dialkyl, diallyl, or diaryl carbonate are contacted at a temperature in arrange from about 80°C to about 150°C.
12. The method according to claim 1, wherein said anhydrosugar compound and said dialkyl, diallyl, or diaryl carbonate are contacted in a neat solution of said dialkyl, diallyl, or diaryl carbonate.
13. The method according to claim 1, wherein said Brønsted base has a pKa of at least 4.

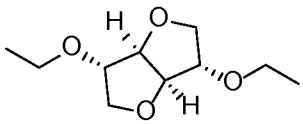
14. The method according to claim 13, wherein said Brønsted base has a pKa 7-14.
15. The method according to claim 1, wherein said Brønsted base is at least one of the following: a carbonate; a hindered amine; a nucleophilic base; a sodium, potassium or calcium hydride; or an organometallic compound.
16. The method according to claim 15, wherein said organometallic compound is an alkyl-lithium or alkyl-magnesium.
17. An ether compound prepared according to the method of claim 1, wherein said ether compound is at least one of the following: a monoalkyl ether or dialkyl ether.
18. The ether compound according to claim 17, wherein said ether compound has a structure:



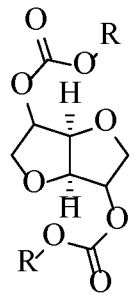
, wherein for a dialkyl ether, R is a C_1-C_3 alkyl group; and, for a monoalkyl ether, one R is a C_1-C_3 alkyl group and another is an OH.

19. The ether compound according to claim 17, wherein said ether compound is at least:

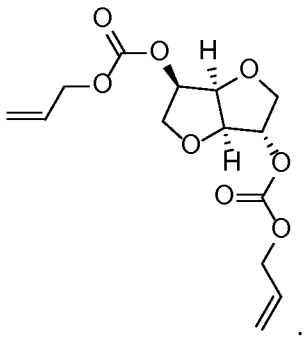
an isoidide monoethylether, with a structure:  ;

an isoidide diethylether, with a structure:  .

20. The alkylated isohexide compound according to claim 17, wherein said compound is an ether selected from the group consisting of: mono-methyl ether of isoiodide; mono-ethyl ethers, of isosorbide, isommanide, or isoiodide, respectively; diethyl ester of isoiodide; mono-propyl ether of isomannide; dipropyl ether of isomannide; mono-propyl ether of isoidide; dipropyl ether of isoiodide; mono-benzyl ether of isoidide; monoallyl ethers of isosorbide, isommanide, or isoiodide, respectively; and diallyl ethers of isosorbide, isommanide, or isoiodide, respectively.
21. A carbonate compound prepared according to the method of claim 1, wherein said carbonate compound is at least one of the following: a mono-alkyl carbonate, dialkyl carbonate, mono- or di-aryl carbonate, mono- or di-allyl carbonate, or a carbonate with an alkyl group from 4-20 carbon atoms.

22. The carbonate compound according to claim 21, wherein said carbonate compound has a structure:  , wherein for a dialkyl carbonate, R is a C_4 or higher carbon alkyl, phenyl, allyl group; and, for a monoalkyl ether, one R is a C_4 or higher carbon alkyl, phenyl, allyl group and another is an OH.

23. The carbonate compound according to claim 21, wherein said carbonate compound is: isosorbide diallyldicarbonate, with a structure:



24. The alkylated isohexide compound according to claim 21, wherein said compound is a carbonate selected from the group consisting of: mono-methylcarbonate of isomannide; mono-methylcarbonate of isoidide; dimethylcarbonate of isomannide; dimethylcarbonate of isoidide; monoethylcarbonates of isosorbide, isommanide, or isoiodide; diethylcarbonate of isomannide; diethylcarbonate of isoidide; mono-propyl or dipropylcarbonates of isosorbide, isommanide, or isoiodide; mono- or dicarbonates having an alkyl R-group of C_4 to C_{20} of isosorbide, isommanide, or isoiodide, respectively; mono-benzyl or dibenzyl carbonates of isosorbide, isommanide, or isoiodide, respectively; monophenylcarbonates of isosorbide, isommanide, or isoiodide, respectively; and diphenylcarbonates of isomannide or isoidide.