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(71) Applicant: **ARCHER DANIELS MIDLAND COMPANY** [US/US]; Corey M. Crafton, 4666 Faries Parkway, Decatur, Illinois 62526 (US).

(72) Inventor: **STENSRUD, Kenneth**; 2017 W. William, Decatur, Illinois 62522 (US).

(74) Agent: **KUNG, Vincent T.**; Archer Daniels Midland Company, 4666 Faries Parkway, Decatur, Illinois 62526 (US).

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(54) Title: PREPARATION OF ISOHEXIDE-3,6-DICARBALDEHYDES AND ISOHEXIDE-3,6-DIMETHANAMINES

(57) Abstract: Methods for synthesizing isohexide-3,6-dicarbaldehydes and/or isohexide-3,6-dimethanamines from the dehydration products of sugar alcohols (isohexides) and corresponding derivatives are described. The methods involve initially converting the -OH moieties of an isohexide into triflates using triflic anhydride at low temperatures, followed by a carbon-centered nitrile-for-triflate substitution, forming crystalline isohexide-3,6-dinitriles. The isohexide-3,6-dinitriles are then reacted with a reducing agent, such as a metal hydride, in an anhydrous organic solvent at very low temperatures to generate isohexide-3,6-dicarbaldehydes. In a subsequent reductive animation, the isohexide-3,6-dicarbaldehydes are first converted into corresponding diimines, which can be isolated, or then reduced to isohexide-3,6-dimethanamines.

PREPARATION OF ISOHEXIDE-3,6-DICARBALDEHYDES AND ISOHEXIDE-3,6-DIMETHANAMINES

FIELD OF INVENTION

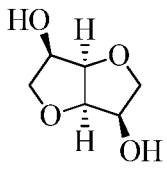
[0001] The present disclosure relates to certain cyclic bifunctional monomers derived from renewable materials. In particular, the present invention pertains to methods for the synthesis of dicarbaldehydes and corresponding methanamines from the dehydration products of sugar alcohols.

BACKGROUND

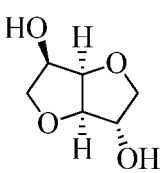
[0002] In recent years, researchers have devoted effort to find ways to employ biomass as economically viable alternative feedstocks to petroleum-based hydrocarbons for the production of organic chemicals because of the relative abundance and renewability of biomass. Biomass contains carbohydrates or sugars that can be converted into value added products. Carbohydrates, however, suffer from discrete shortcomings. In contrast to petroleum-based hydrocarbon molecules, which contain limited or lesser amounts of functional groups, carbohydrates such as polysaccharides are markedly complex, over-functionalized hydrophilic materials. Carbohydrates contain many -OH functionality which limits interactive capacities in, for example, non-aqueous media, as well as exhibit a tendency to degrade under traditional high temperature processes. Hence, recent research has concentrated on generating biomass-derived chemicals that are prepared solely from carbohydrates, but which are less highly functionalized, including more stable bi-functional compounds, such as 2,5-furandicarboxylic acid (FDCA), levulinic acid, and 1,4:3,6-dianhydrohexitols.

[0003] 1,4:3,6-Dianhydrohexitols (referred henceforth as isohexides) are molecular species that embody a class of bicyclic tetrahydrofuranodiols, which are prepared from corresponding reduced sugar alcohols (D-sorbitol, D-mannitol, and D-iditol respectively). Depending on the two -OH group orientations, three isomers of the isohexides exist, namely: A) isomannide, B) isosorbide, and C) isoidide, respectively; the structures of which are illustrated in Scheme A.

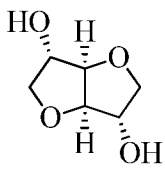
Scheme A: Structures of isomannide A, isosorbide B, and isoidide C.



A



B



C

[0004] Interest in isohexides as chemical substrates has been increasing in recent years in part because of the relative low cost of the starting compounds, their relative ease of preparation and

purification, and the *sui generis*, two-fold chirality of these molecules. This characteristic allows one to synthesize a multitude of potential derivatives. For instance in the field of polymeric materials, industrial uses for these diols as monomers have been explored. Particularly alluring attributes of these monomers are associated with their inherent rigidity, chirality, and non-toxicity. These features makes the molecules attractive for the synthesis of high glass transition temperature polymers with good thermo-mechanical resistance and/or with special optical properties. Furthermore, the intrinsic durability of these platforms allows for applications in packaging or medical devices. (*See e.g.*, F. Fenouillot *et al.*, "Polymers From Renewable 1,4:3,6-Dianhydrohexitols (Isosorbide, Isomannide 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, *J. Am. Chem. Society*, Dec. **2010**, contents of which are incorporated herein by reference.) Some other potentially useful compounds from isohexide-derived polymers may include, for example, polyesters, polyamides, and polyurethanes.

[0005] Given the potential uses, a cost efficient and simple process that can make isohexide-3,6-dicarbaldehydes or 3,6-dimethanamines more accessible and easily manipulated for preparation of derivative would be appreciated by manufacturers of both industrial and specialty chemicals alike as a way to better utilize biomass-derived carbon resources.

SUMMARY OF INVENTION

[0006] The present disclosure describes, in part, a straightforward method for making either isohexide-3,6-dicarbaldehydes or 3,6-dimethanamines. In general, the method involves transforming, initially, an isohexide into an isohexide-3,6-dinitrile, then providing a reaction mixture containing isohexide-3,6-dinitriles and an anhydrous, inert, organic solvent, contacting the isohexide-3,6-dinitriles with a reducing agent at a reaction temperature for a time sufficient to produce the isohexide-3,6-dicarbaldehyde. The method may further involve contacting the isohexide-3,6-dicarbaldehyde with an aminating agent under a reducing condition to generate isohexide-3,6-dimethanamines.

[0007] In another aspect, the disclosure pertains to a method of preparing an isohexide derivative compound of an isohexide-3,6-dicarbaldehyde. The method involves reacting a mixture containing isohexide-3,6-dinitriles, and an inert organic solvent and a reducing agent at a reaction temperature between about -50°C to about -100°C, forming an isohexide-3,6-dicarbaldehyde, and then transforming the isohexide-3,6-dicarbaldehyde into a dimethanimine or dimethanamine. Alternatively, according to an embodiment the method may be further adapted to prepare a derivative compound of an isohexide-3,6-dimethanamine, after reductive amination of the isohexide-3,6-dicarbaldehyde. For instance, amidating the isohexide-3,6-dimethanamine to generate a polyamide.

[0008] Additional features and advantages of the present synthesis 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 INVENTION

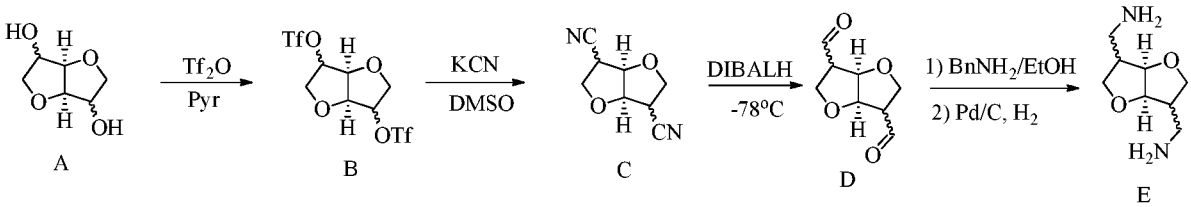
Section I – Description

A. Preparation of Isohexide-3,6-Dicarbaldehydes and Isohexide-3,6-Dimethanamines

[0009] The present invention describes, in part, an efficient and simple process for synthesizing isohexide-3,6-dicarbaldehydes and isohexide-3,6-dimethanamines from 1,4:3,6-dianhydrohexitols (referred to as "isohexides" in the Description hereinafter). Each of these types of molecules can serve as valuable chemical substrates or precursor molecules in the preparation of a variety of potential chemical compounds, including for instance, chiral auxillaries (asymmetic synthesis used in pharmaceutical production), surfactants, solvents, acrylics and other polymeric materials.

[0010] To take advantage of the utility of isohexides as renewable molecular platforms, the present process involves a short sequence of mild, high-yielding synthesis operations. Scheme 1 presents an illustration of the present synthesis method according to an embodiment to make an isohexide-3,6-dicarbaldehyde, and then isohexide-3,6-dimethanamine.

Scheme 1.

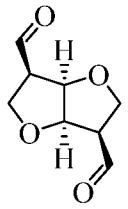


As depicted, an isohexide (A) is first transformed into its corresponding isohexide-3,6-dinitrile (C). The isohexide can be any one of the sugar alcohols – isomannide, isosorbide, or isoidide. The process is initiated by a triflate nucleofugation of the -OH moieties of the isohexide. An isohexide and triflic anhydride are reacted in a pyridine-rich matrix forming an isohexide di-triflate (B), followed by a carbon-centered nitrile-for-triflate substitution, underscored by a Walden inversion. (For preparation of isohexide-3,6-dinitriles *cf.*, International Publication No. WO2013/173020 A1 (Int'l Application No. PCT/US2013/037098), the contents of which are incorporated herein by reference in its entirety.) In a subsequent operation, the synthesis involves providing a reaction mixture containing the isohexide-3,6-dinitrile and an anhydrous, inert, organic solvent, and reacting the isohexide-3,6-dinitrile (C) with a reducing agent at a reaction temperature for a time sufficient to produce the isohexide-3,6-dicarbaldehyde (D). This transformation occurs typically at low temperatures through a hydride-mediated cascade imine capture and hydrolysis to generate the isohexide-3,6-dicarbaldehydes (D). Lastly, in a subsequent reductive animation (e.g., employing mild benzylamine/catalytic

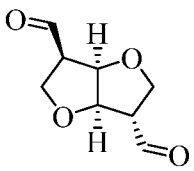
hydrogenation) the isohexide-3,6-dicarbaldehydes are first converted into corresponding diimines, which can be isolated, or reduced to the dimethamamine analog (E).

[0011] Scheme 2 presents the structures of the corresponding resultant isohexide-3,6-dicarbaldehyde for isomannide, isosorbide, and isoidide starting materials: isomannide-3,6-dicarbaldehyde **1**, isosorbide-3,6-dicarbaldehyde **2**, and isoidide-3,6-dicarbaldehyde **3**.

Scheme 2.



1



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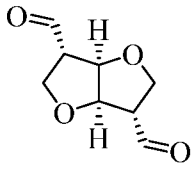
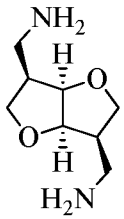


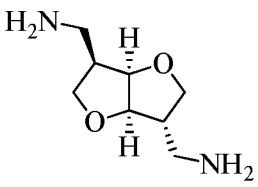
3

After reductive amination of these aldehydes, Scheme 3 shows the corresponding structures of isomannide-3,6-dimethanamine **A,** isosorbide-3,6-dimethanamine **B**, and isoidide-3,6-dimethanamine **C**.

Scheme 3.



A



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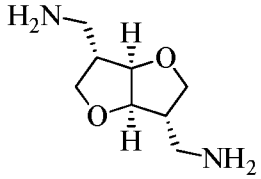

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[0012] The present process is able to produce primarily isohexide-3,6-dicarbaldehydes in reasonably high yields of at least 47 mol.% from the isohexide-3,6-dinitrile starting materials and subsequently the isohexide-3,6-dimethanamines in yields of at least 68 mol.% from the isohexide-3,6-dicarbaldehydes. Typically, the yield of isohexide-3,6-dicarbaldehyde is in a range from about 50 mol.% or 55 mol.% to about 75 mol.% or 80 mol.% (e.g., 57%, 60%, 63%, 65%, 68%, 70%, 72%, 78%); with optimization of the process the yield can achieve about 85 mol.% to 90 mol.% or 93 mol.% or greater. The yield of the isohexide-3,6-dimethanamine is in a range from about 70 mol.% or 75 mol.% to about 85 mol.% or 95 mol.% (e.g., 72%, 78%, 80%, 83%, 88%, 90%, 92%).

[0013] According to certain embodiments, the initial reductive step involves reaction of an isohexide-3,6-dinitrile and a sterically-hindered metal hydride in an inert solvent at a temperature from about -70°C to about -80°C, followed by an aqueous workup to quench excess hydride. The resultant isohexide-3,6-dicarbaldehydes are then iminated with benzylamine at a temperature from about -5°C to -20°C in absolute ethanol, followed by catalytic hydrogenation in the unperturbed matrix, to generate the isohexide-3,6-dimethanamines.

[0014] In the embodiment shown in Scheme 1, the reducing agent is diisobutylaluminium hydride (DIBALH). Some other metal hydrides may include, for example, sodium borohydride and lithium aluminum hydride. When using the hindered reducing agent, DIBAL-H, one benefits from a very low temperature (about -78°C) to preclude imine reduction before hydrolysis. In other embodiments, one can add tin (II) chloride and aqueous HCl simultaneously to a solution of the dinitrile to convert it to the corresponding dialdehyde according to the Stephen synthesis. In yet another reaction protocol, one can reduce the nitrile with hydrogen, followed by the concurrent hydrolysis of an intermediate imine. Other reducing agents that can be used in this transformation are heterogeneous catalysts, such as Raney nickel or sponge copper. When using the Stephens synthesis (tin (II) chloride, HCl) or Raney nickel hydrogenation, room temperature or higher is preferred.

[0015] The reduction reaction should be performed at an extremely low temperatures that range from about -50°C to about -100°C. Typically, the temperature range is from about -55°C or -60°C to about -85°C or -90°C, more typically the range is from about -65°C to about -80°C (e.g., -70°C, -75°C, or -78°C). Such low temperatures help to moderate the reaction. The kinetics of the process enables the dialdehydes to be isolated at low temperatures; elevated temperatures result in the abrupt reduction of imine intermediates before hydrolysis can occur, generating the thermodynamically favored diamines.

[0016] The inert organic solvent is a polar and aprotic solvent species. Some solvents can have a melting point below -90°C; such organic solvents may include tetrahydrofuran (THF), methylene chloride, or diethyl ether. Alternatively, in other embodiments where one may apply higher temperatures, the solvents may include, for example, dimethylformamide (DMF), dimethylacetamide (DMA), 1,4-dioxane, or toluene.

[0017] For the animation operation, benzylamine ($BnNH_2$) is a favored reactant as it is stable and a facile primary amine precursor. The benzyl group is removed easily by hydrogenation under mild conditions. Other reagents that can generate amines may include aqueous ammonia or ammonium chloride ammonia. Ammonia is less favored to use, however, owing to its corrosiveness.

[0018] Amination can be performed under ambient temperatures in a range from about 10°C to about 50°C (e.g., 12°C, 15°C, 18°C, 20°C, 22°C, 25°C, 30°C, 32°C, 35°C, 40°C, or 45°C).

[0019] In the benzylamine reduction to primary amine, one may employ ethanol as the solvent, but methanol, ethyl acetate, THF, DMF, dimethyl sulfoxide (DMSO) can also be used. Alternatively, one may also use heterogeneous catalysts such as Ru/C, Pt/C, Pd/C, and Raney Ni with H_2 gas to reduce benzylamine to primary amines.

B. Preparation of Derivatives Compounds from Isohexide-3,6-Dicarbaldehyde and Isohexide-3,6-Dimethanamine

[0020] In another aspect of the present invention, the isohexide-3,6-dicarbaldehydes and isohexide-3,6-dimethanamines can be modified to generate functionalized materials that can be useful as

precursors for making other chemical compounds, such as polymers, lubricants, surfactants, additives, and dispersants.

[0021] According to an embodiment, a method of preparing an isohexide derivative compound involves: reacting a solution containing isohexide-3,6-dinitriles, and an inert organic solvent with a (sterically-hindered) reducing agent at a reaction temperature between about -50°C to about -100°C; forming an isohexide-3,6-dicarbaldehyde; and transforming said isohexide-3,6-dicarbaldehyde into other bicyclic tetrahydrofuranic derivative compounds. The transformation may entail performing either 1) a reductive amination and polymerization, or 2) a bis-allylation and glycolation on the isohexide-3,6-dicarbaldehyde.

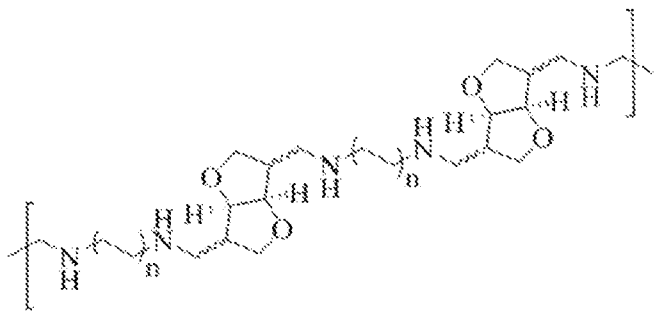
[0022] To prepare polyamines, the isohexide-3,6-dicarbaldehyde is reacted with a dialkyl amine (e.g., dibutylamine in the paradigm shown in Scheme 5, below) at room temperature, generating a polyimine precursor, which is then hydrogenated under mild conditions, effectively reducing the imine moieties to the corresponding amine.

[0023] To prepare diallyl analogs of isohexide-3,6-dicarbaldehyde, Grignard reagents are used. A favored and feasible route to produce diallyl analogs is to deploy allyl magnesium bromide as the Grignard reagent, reacting with a stoichiometric amount of dialdehyde at a temperature in the range from about -65°C to about -85°C (e.g., -75°C, -78°C, -80°C) then quenching the reaction with water. As a relatively inexpensive and commercially available reagent, allyl magnesium bromide is used in a typical embodiment. Other potential Grignard reagents can include allyl magnesium chloride and allyl magnesium iodide.

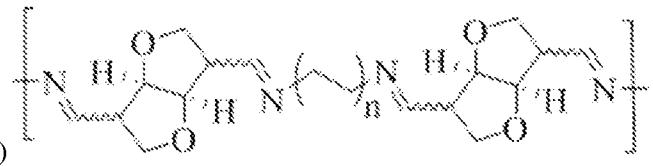
[0024] The resulting isohexide-3,6-dicarbaldehyde derivative compound respectively from each reaction can be either a) diaminohexane-isohexide or diiminohexane-isohexide polymer or b) diallyl-glycols. Scheme 4 A1), A2) and B) respectively depict the general structure of each of these compounds.

Scheme 4.

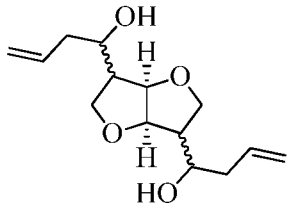
A1)



A2)

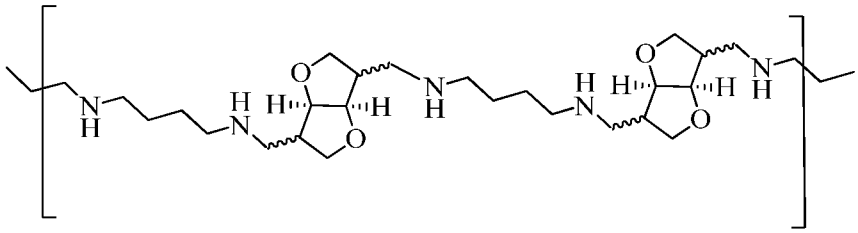


A3)

B) 

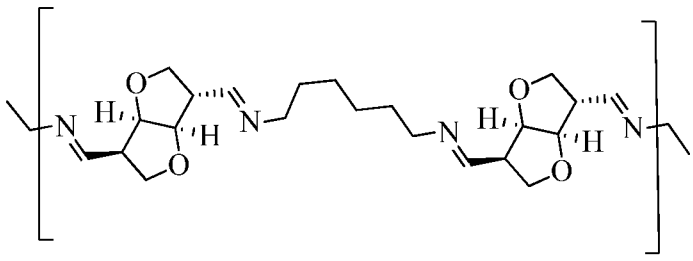
[0025] Scheme 5 shows an example of a particular compound formed of the polymerization of isohexide-3,6-di-dicarbaldehyde and dibutylamine.

Scheme 5.

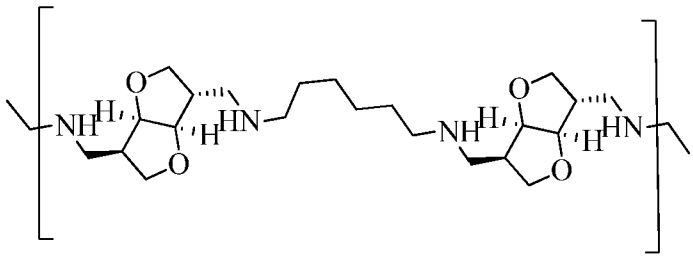


[0026] Other examples of particular isohexide-3,6-dicarbaldehyde derivative compounds may include at least one of the following:

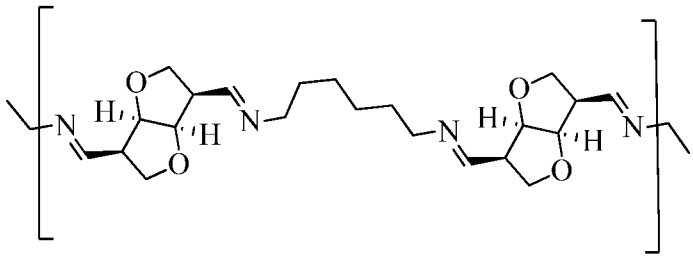
1) an isosorbide-hexanimine polymer



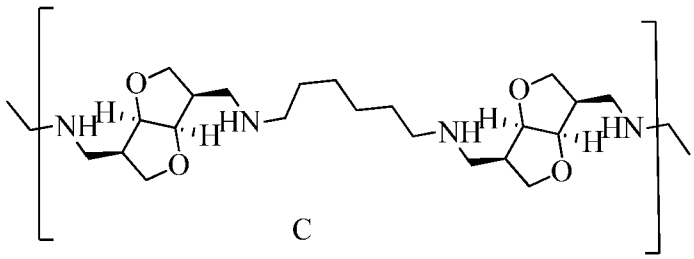
2) an isosorbide-hexanamine polymer



3) an isomannide-hexanimine polymer



4) an isomannide-hexanamine polymer



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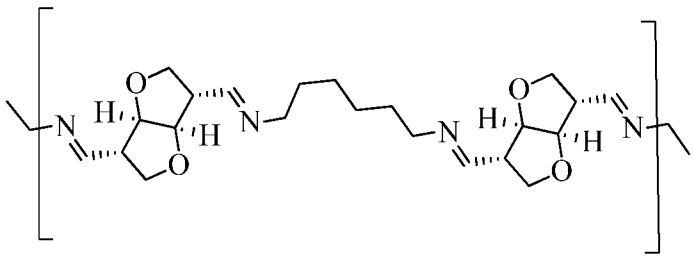
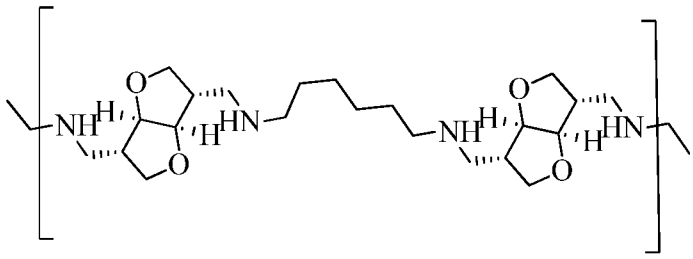


5) an isoidide-hexanimine polymer

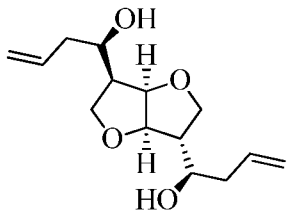
;

6) an isoidide-hexanamine polymer



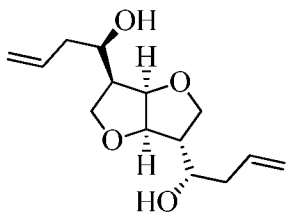
;

7) (1R,1'R)-1,1'-((3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(but-3-en-1-ol)



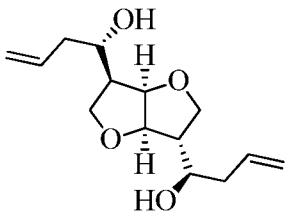
;

8) (1S,1'R)-1,1'-((3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(but-3-en-1-ol)



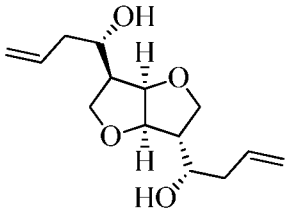
;

9) (1R,1'S)-1,1'-((3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(but-3-en-1-ol)



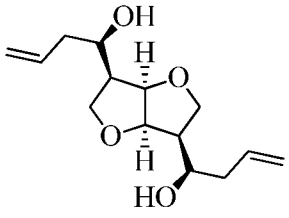
;

10) (1S,1'S)-1,1'-((3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(but-3-en-1-ol)



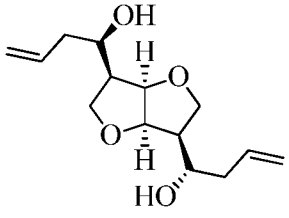
;

11) (1R,1'R)-1,1'-((3S,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(but-3-en-1-ol)



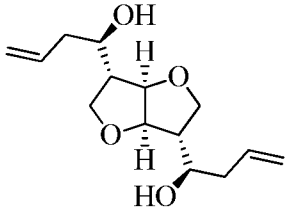
;

12) (1S,1'R)-1,1'-((3S,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(but-3-en-1-ol)



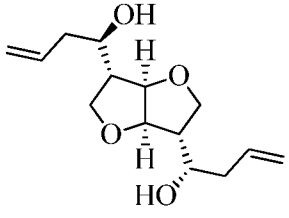
;

13) (1R,1'R)-1,1'-((3R,3aR,6R,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(but-3-en-1-ol)



;

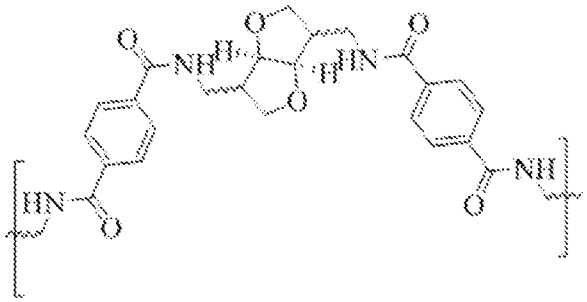
14) (1S,1'R)-1,1'-((3R,3aR,6R,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(but-3-en-1-ol)



.

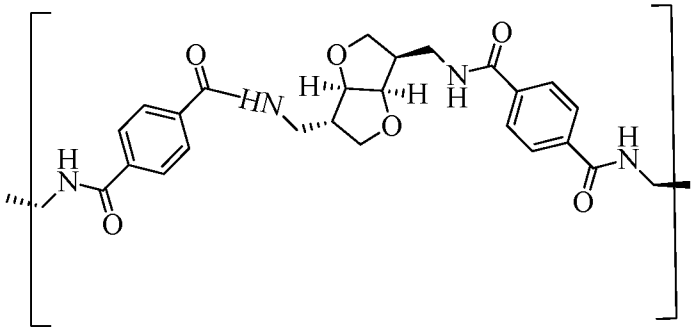
[0027] To prepare terephthalic-isohexide amine polymers, terephthaloyl chloride is reacted with isohexide diamines at room temperature for a short time. The polymers will likely precipitate from solution when the polymeric molecular weight reaches a sufficient magnitude. Terephthaloyl chloride is very reactive and can generate significantly high yields of amide polymers. Alternatively, one could use a dimethyl ester to achieve amidation, but under such an approach the reaction usually will require employing harsher conditions and will tend to generate more side product. Scheme 6 shows the general structure of an isohexide-3,6-diamine-terephthalate polyamide.

Scheme 6.



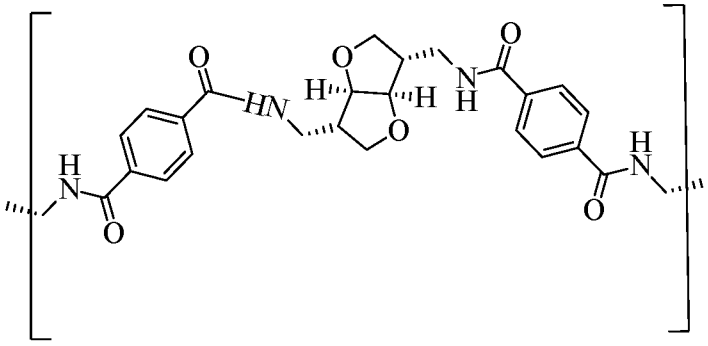
[0028] Examples of some particular terephthalic-isohexide amine polymers may include at least one of the following:

1) an isomannide-3,6-diamine-terephthalate polyamide



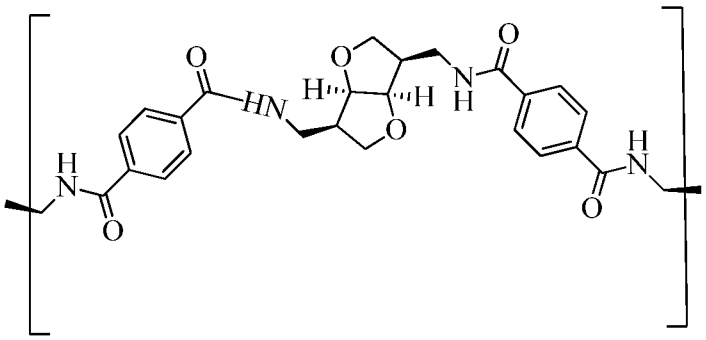
;

2) an isoidide-3,6-dimethanamine-terephthalate polyamide



;

3) an isosorbide-3,6-dimethanamine-terephthalate polyamide



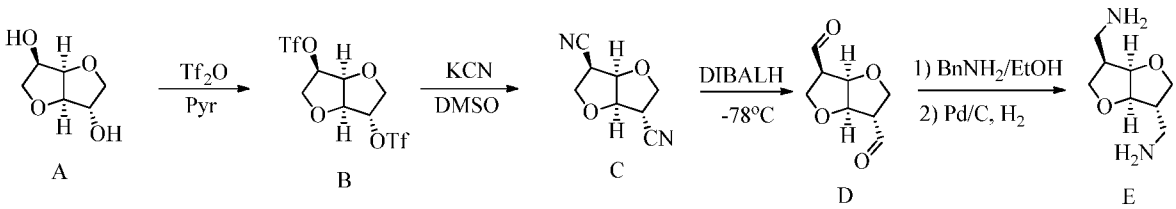
[0029] Illustrative embodiments of the methods for preparing the foregoing derivatives and other compounds are further described in detail in the following examples.

Section II – Examples

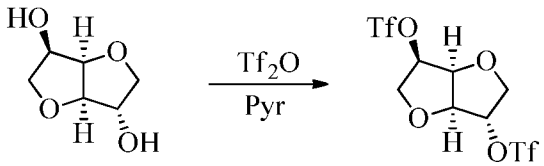
I. – Preparation of Isohexide-3,6-Dicarbaldehyde and Isohexide-3,6-Dimethanamine

[0030] The following examples further demonstrate the individual reactions in the synthesis of isohexide-3,6-dicarbaldehyde species according to the present method, and reductive amination of these aldehydes to generate the corresponding isohexide-3,6-dimethanamines.

[0031] A. Preparation of (3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-dicarbaldehyde, **D** (Isosorbide-3,6-dicarbaldehyde).



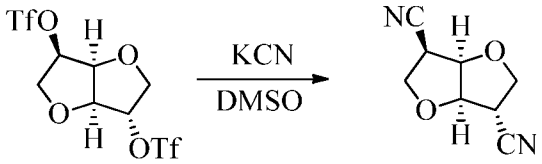
[0032] Example 1: Synthesis of (3R,3aS,6S,6aS)-hexahydrofuro[3,2-b]furan-3,6-diyl bis-(trifluoromethane-sulfonate), **B**.



Experimental: A flame-dried, single neck 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 200 mg of isosorbide **A** (1.37 mmol), 553 µL pyridine (6.84 mmol), and 5 mL of anhydrous methylene chloride. The flask was then immersed in a saturated brine/ice bath (reading -10°C), and after 15 minutes, with vigorous stirring, 691 µL of triflic anhydride (4.11 mmol) was added dropwise over 20 minutes. Once added, the brine bath was removed and stirring continued overnight. After this time, 2 mL of water was added to quench unreacted triflate, then the mixture concentrated via rotary evaporation (50°C, 30 torr). The dark

viscous residue was taken up in a minimum amount of methylene chloride, then charged to a prefabricated silica gel column, where gradient flash chromatography with hexanes/ethyl acetate eluent afforded 401 mg of **B** (3:1 hexanes/ethyl acetate) as a pale yellow, loose oil after concentration under high vacuum (71% of theoretical). Spectroscopic analysis of this material was consistent with that published in WO 2013173020 A1 20131121.

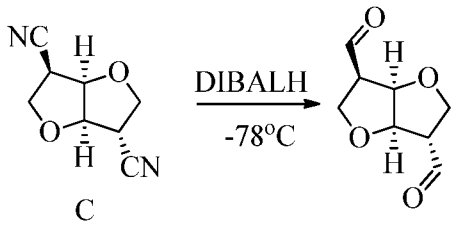
[0033] Example 2: Synthesis of (3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-dicarbonitrile, **C**.



B C

Experimental: A flame-dried, single neck 50 mL round equipped with a PTFE coated magnetic stir bar was charged with 300 mg of **B** (0.731 mmol), 190 mg potassium cyanide (2.92 mmol), and 20 mL of anhydrous dimethyl sulfoxide (DMSO). The mixture was stirred vigorously at room temperature for 48 hours. After this time, the solids were vacuum filtered through a CELITE™ pad and filtrate concentrated *in vacuo* for an additional day. After this time, the dark viscous oil was taken up in a minimum amount of methylene chloride and charged to a prefabricated silica gel column, where chromatography with hexanes/ethyl acetate eluent (1:1 hexanes/ethyl acetate) afforded 80 mg of **C** as a pale yellow oil (67% of theoretical). Spectroscopic analysis of this material was consistent with that published in WO 2013173020 A1 20131121.

[0034] Example 3: Synthesis of (3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-dicarbaldehyde, **D**.

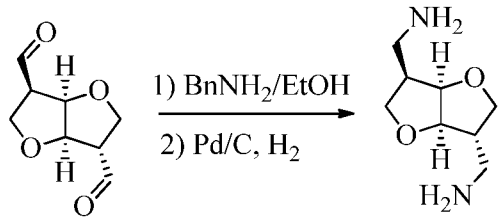


C D

Experimental: A flame-dried, single neck 5 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 75 mg of **C** (0.457 mmol) and 2 mL of anhydrous methylene chloride. The flask was capped with a rubber septum affixed to an argon inlet via a stainless steel 16" needle, and then immersed in a saturated dry ice/acetone bath (-78°C). While stirring and under an argon blanked, 1 mL of diisobutylaluminumhydride (DIBAL-H, 1M in hexanes), was added dropwise over a 10 minutes interval and the reaction continued for two more hours at -78°C. After this time, 1 mL of water was added to quench excess hydride, and the resultant mixture poured directly onto a prefabricated silica gel column, where gradient flash chromatography with hexanes/ethyl acetate

eluent furnished 39.6 mg of **D** after concentration (51% of theoretical). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.61 (s, 1H), 9.59 (s, 1H), 4.41 (m, 2H), 4.03 (m, 2H), 3.96 (m, 2H), 3.32 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.1, 201.9, 93.0, 92.8, 66.0, 65.2, 53.4, 53.1.

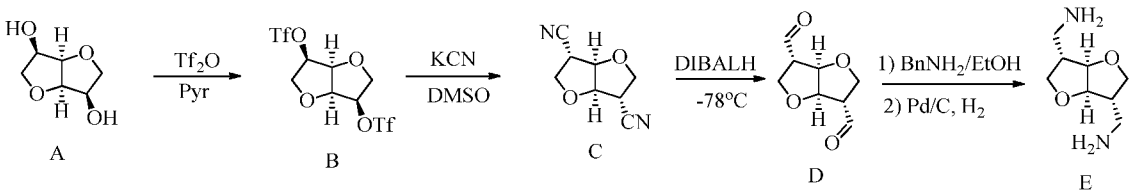
[0035] Example 4. Synthesis of ((3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)dimethanamine **E**.



D E

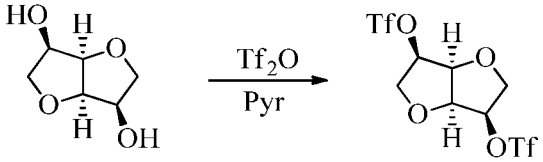
Experimental: An oven dried, 5 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 25 mg of **D** (0.147 mmol) and 2 mL of absolute ethanol. The flask was capped with a rubber septum and immersed in a saturated brine/ice bath (-10°C) for 15 minutes. While stirring, 32 mg of benzyl bromide (0.295 mmol) added dropwise over 10 minutes. Once the amine had been added, the ice bath was removed and reaction continued at room temperature for an additional 4 hours. After this time a 25 mg of 10% Pd/C was added, and balloon filled with H_2 was affixed to the septum via a 16" needle. The flask head space was purged with two balloon volumes of H_2, followed by one volume that channeled through the needle. The reaction mixture was stirred under the H_2 blanket for 4 hours, then filtered through a CELITE™ pad. Surplus solvent evaporation using a rotary evaporator (40°C, 35 torr), then high vacuum (<5 torr), furnished 20 mg of **E** as a light yellow semi-solid (80% of theoretical). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.79 (m, 4H), 3.95 (m, 2H), 3.62 (m, 2H), 3.55 (m, 2H), 2.92 (m, 2H), 2.61 (m, 2H), 2.37 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ (ppm) 89.1, 88.7, 67.5, 66.8, 43.0, 42.7, 37.9, 37.6.

[0036] B. Preparation of (3S,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-dicarbaldehyde, **D** (Isoidide-3,6-dicarbaldehyde)



A B C D E

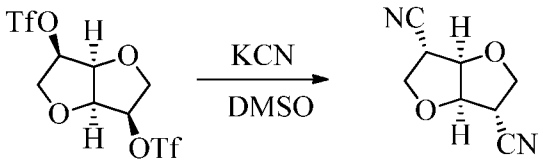
[0037] Example 1: Synthesis of (3R,3aS,6R,6aS)-hexahydrofuro[3,2-b]furan-3,6-diyl bis(trifluoromethane-sulfonate), **B**.



A B

Experimental: A flame-dried, single neck 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 200 mg of isomannide **A** (1.37 mmol), 553 µL pyridine (6.84 mmol), and 5 mL of anhydrous methylene chloride. The flask was then immersed in a saturated brine/ice bath (reading -10°C), and after 15 minutes, with vigorous stirring, 691 µL of triflic anhydride (4.11 mmol) was added dropwise over 20 minutes. Once added, the brine bath was removed and stirring continued overnight. After this time, 2 mL of water was added to quench unreacted triflate, then the mixture concentrated via rotary evaporation (50°C, 30 torr). The dark viscous residue was taken up in a minimum amount of methylene chloride, then charged to a prefabricated silica gel column, where gradient flash chromatography with a hexanes/ethyl acetate eluent afforded 422 mg of **B** (4:1 hexanes/ethyl acetate) as a yellow, loose oil after concentration under high vacuum (75% of theoretical). Spectroscopic analysis of this material was consistent with that published in WO 2013173020 A1 20131121, the contents of which are incorporated herein by reference.

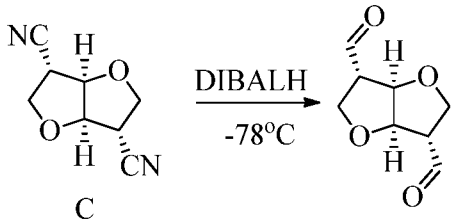
[0038] Example 2: Synthesis of (3S,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-dicarbonitrile, **C**.



B C

Experimental: A flame-dried, single neck 50 mL round equipped with a PTFE coated magnetic stir bar was charged with 300 mg of **B** (0.731 mmol), 190 mg potassium cyanide (2.92 mmol), and 20 mL of anhydrous DMSO. The mixture was stirred vigorously at room temperature for 48 hours. After this time, the solids were vacuum filtered through a CELITE™ pad and filtrate concentrated *in vacuo* for an additional day. After this time, the dark viscous oil was taken up in a minimum amount of methylene chloride and charged to a prefabricated silica gel column, where chromatography with hexanes/ethyl acetate eluent (1:1 hexanes/ethyl acetate) afforded 71 mg of **C** as a pale yellow oil (59% of theoretical). Spectroscopic analysis of this material was consistent with that published in WO 2013173020 A1 20131121, the contents of which are incorporated herein by reference.

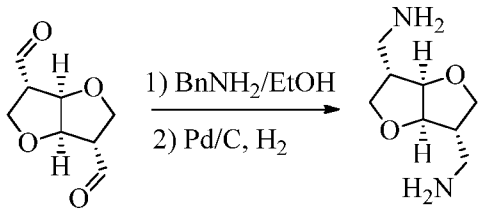
[0039] Example 3: Synthesis of (3S,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-dicarbaldehyde, **D**.



C D

Experimental: A flame-dried, single neck 5 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 60 mg of **C** (0.366 mmol) and 2 mL of anhydrous methylene chloride. The flask was capped with a rubber septum affixed to an argon inlet via a stainless steel 16" needle, and then immersed in a saturated dry ice/acetone bath (-78°C). While stirring and under an argon blanked, 1 mL of diisobutylaluminumhydride (DIBAL-H, 1M in hexanes), was added dropwise over a 10 minutes interval and the reaction continued for two more hours at -78°C. After this time, 1 mL of water was added to quench excess hydride, and the resultant mixture poured directly onto a prefabricated silica gel column, where gradient flash chromatography with hexanes/ethyl acetate eluent furnished 28.8 mg of **D** after concentration (47% of theoretical). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.61 (s, 2H), 4.41 (m, 2H), 4.19 (m, 2H), 3.98 (m, 2H), 3.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.3, 92.8, 65.8, 53.4.

[0040] Example 4: Synthesis of ((3S,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)dimethanamine, **E**.

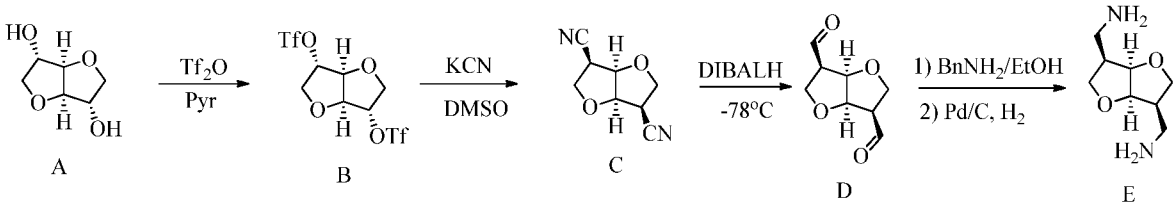


D E

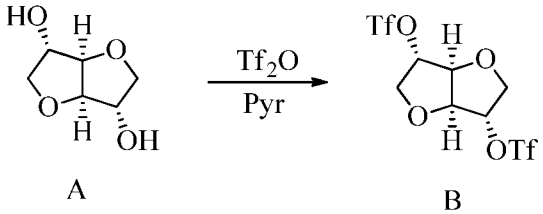
Experimental: An oven dried, 5 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 25 mg of **D** (0.147 mmol) and 2 mL of absolute ethanol. The flask was capped with a rubber septum and immersed in a saturated brine/ice bath (-10°C) for 15 minutes. While stirring, 32 mg of benzyl bromide (0.295 mmol) added dropwise over 10 minutes. Once the amine had been added, the ice bath was removed and reaction continued at room temperature for an additional 4 hours. After this time a 25 mg of 10% Pd/C was added, and balloon filled with H_2 was affixed to the septum via a 16" needle. The flask head space was purged with two balloon volumes of H_2, followed by one volume that channeled through the needle. The reaction mixture was stirred under the H_2 blanket for 4 hours, then filtered through a CELITE™ pad. Surplus solvent evaporation using a rotary evaporator (40°C, 35 torr), then high vacuum (<5 torr), furnished 18 mg of **E** as a light yellow semi-solid (72% of theoretical). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.82 (m, 4H), 3.92(m,

2H), 3.57 (m, 2H), 3.52 (m, 2H), 2.90 (m, 2H), 2.59 (m, 2H), 2.33 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ (ppm) 89.3, 67.1, 43.4, 37.7.

[0041] C. Preparation of (3R,3aR,6R,6aR)-hexahydrofuro[3,2-b]furan-3,6-dicarbaldehyde, **D** (Isomannide-3,6-dicarbaldehyde)

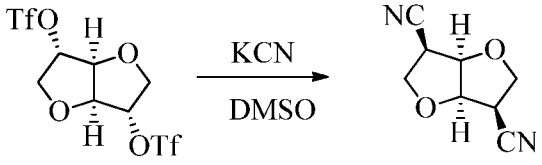


[0042] Example 1: Synthesis of (3S,3aS,6S,6aS)-hexahydrofuro[3,2-b]furan-3,6-diyl bis(trifluoromethane-sulfonate), **B**.



Experimental: A flame-dried, single neck 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 200 mg of isoidide **A** (1.37 mmol), pyridine (6.84 mmol) 553 µL, and 5 mL of anhydrous methylene chloride. The flask was then immersed in a saturated brine/ice bath (reading -10°C), and after 15 minutes, with vigorous stirring, 691 µL of triflic anhydride (4.11 mmol) was added dropwise over 20 minutes. Once added, the brine bath was removed and stirring continued overnight. After this time, 2 mL of water was added to quench unreacted triflate, then the mixture concentrated via rotary evaporation (50°C, 30 torr). The dark viscous residue was taken up in a minimum amount of methylene chloride, then charged to a prefabricated silica gel column, where gradient silica gel chromatography with hexanes/ethyl acetate eluent afforded 383 mg of **B** (3:1 hexanes/ethyl acetate) as a colorless, loose oil after concentration under high vacuum (68% of theoretical). Spectroscopic analysis of this material was consistent with that published in WO 2013173020 A1 20131121, the contents of which are incorporated herein by reference.

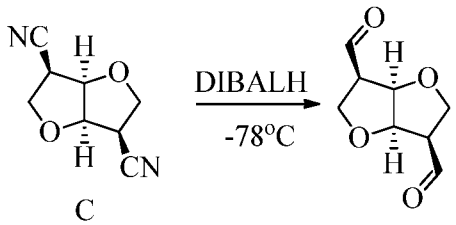
[0043] Example 2: Synthesis of (3R,3aR,6R,6aR)-hexahydrofuro[3,2-b]furan-3,6-dicarbonitrile, **C**.



B C

Experimental: A flame-dried, single neck 50 mL round equipped with a PTFE coated magnetic stir bar was charged with 300 mg of **B** (0.731 mmol), 190 mg potassium cyanide (2.92 mmol), and 20 mL of anhydrous DMSO. The mixture was stirred vigorously at room temperature for 48 hours. After this time, the solids were vacuum filtered with a CELITE™ pad and filtrate concentrated *in vacuo* for an additional day. After this time, the dark viscous oil was taken up in a minimum amount of methylene chloride and charged to a prefabricated silica gel column, where chromatography with hexanes/ethyl acetate eluent (1:1 hexanes/ethyl acetate) afforded 76 mg of **C** as a pale yellow oil (63% of theoretical). Spectroscopic analysis of this material was consistent with that published in WO 2013173020 A1 20131121, the contents of which are incorporated herein by reference.

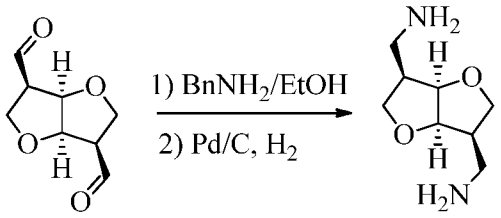
[0044] Example 3: Synthesis of (3R,3aR,6R,6aR)-hexahydrofuro[3,2-b]furan-3,6-dicarbaldehyde, **D**.



C D

Experimental: A flame-dried, single neck 5 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 70 mg of **C** (0.427 mmol) and 2 mL of anhydrous methylene chloride. The flask was capped with a rubber septum affixed to an argon inlet via a stainless steel 16" needle, and then immersed in a saturated dry ice/acetone bath (-78°C). While stirring and under an argon blanked, 1 mL of diisobutylaluminumhydride (DIBAL-H, 1M in hexanes), was added dropwise over a 10 minutes interval and the reaction continued for two more hours at -78°C. After this time, 1 mL of water was added to quench excess hydride, and the resultant mixture poured directly onto a prefabricated silica gel column, where gradient flash chromatography with hexanes/ethyl acetate eluent furnished 36.2 mg of **D** after concentration (50% of theoretical). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.59 (s, 2H), 4.36 (m, 2H), 4.15 (m, 2H), 3.96 (m, 2H), 3.33 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.0, 92.9, 66.1, 53.1.

[0045] Example 4. Synthesis of ((3R,3aR,6R,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)dimethanamine, **E**.



D E

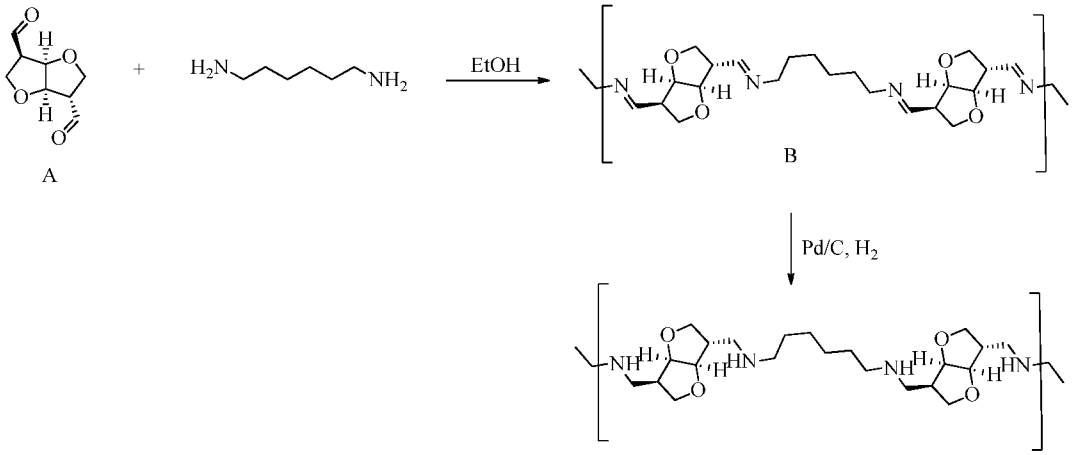
Experimental: An oven dried, 5 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 25 mg of **D** (0.147 mmol) and 2 mL of absolute ethanol. The flask was capped with a rubber septum and immersed in a saturated brine/ice bath (-10°C) for 15 minutes. While stirring, 32 mg of benzyl bromide (0.295 mmol) added dropwise over 10 minutes. Once the amine had been added, the ice bath was removed and reaction continued at room temperature for an additional 4 hours. After this time a 25 mg of 10% Pd/C was added, and balloon filled with H_2 was affixed to the septum via a 16" needle. The flask head space was purged with two balloon volumes of H_2, followed by one volume that channeled through the needle. The reaction mixture was stirred under the H_2 blanket for 4 hours, then filtered through a CELITE™ pad. Surplus solvent evaporation using a rotary evaporator (40°C, 35 torr), then high vacuum (<5 torr), furnished 17 mg of **E** as a light yellow semi-solid (68% of theoretical). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 4.85 (m, 4H), 3.90 (m, 2H), 3.61 (m, 2H), 3.54 (m, 2H), 2.81 (m, 2H), 2.55 (m, 2H), 2.39 (m, 2H); ^{13}C (100 MHz, $CDCl_3$) δ (ppm) 89.8, 67.7, 42.9, 38.3.

II. – Derivatives of Isohexide-3,6-Dicarbaldehyde

[0046] The following examples illustrate the preparation of certain derivative compounds from isohexide-3,6-dicarbaldehyde.

A. Oligomers/polymers of isohexide-3,6-dicarbaldehydes

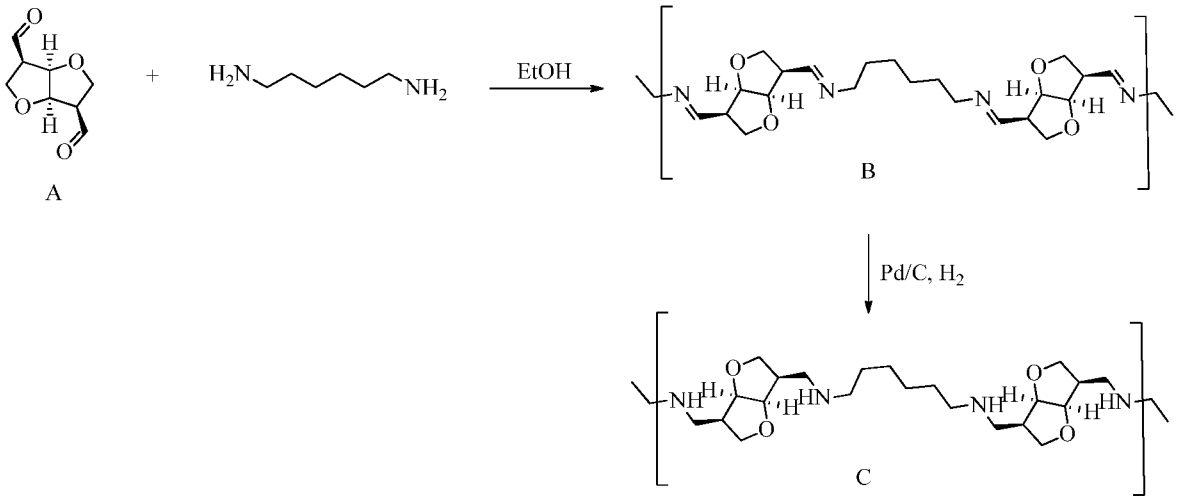
[0047] Example 1.: Synthesis of diiminohexane-isosorbide **B** and diaminohexane **C** oligomers from isosorbide-3,6-dicarbaldehyde **A** and 1,6-diaminohexane.



A B

Experimental: A single neck, 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 25 mg of isosorbide-3,6-dicarbaldehyde (0.147 mmol), 17 mg of 1,6-hexanediamine and 2 mL of ethanol. The mixture was stirred overnight at room temperature. After this time, excess solvent was removed via rotary evaporation (40°C, 35 torr), and then placed under high vacuum for 2 days, affording 41.1 mg of a pale yellow wax. This material was re-dissolved in 2 mL of ethanol and placed into a 50 cc Parr reactor vessel. 25 mg of 10% Pd/C was then added, the vessel sealed, and charged with 200 psi H_2. The mixture was stirred for 2 hours at room temperature, after which the vessel vented, and catalyst filtered over a CELITE™ pad. The filtrate was then inspissated under reduced pressure, furnishing 40.2 mg a transparent solid material, presumably target C. Approximately 5 mg of this was dissolved in 0.750 mL of d^6-DMSO and analyzed by NMR. ^1H NMR revealed broad signals with expected chemical shifts, though integrations proved to be too cumbrous to interpret. ^{13}C NMR provided sharp, definable signals (400 MHz, d^6-DMSO) δ (ppm) 90.3, 87.3, 70.4, 69.7, 69.1, 50.5, 46.3, 44.2, 41.6, 38.1, 31.2, 30.6, 29.3, 28.7, 27.1, 26.5.

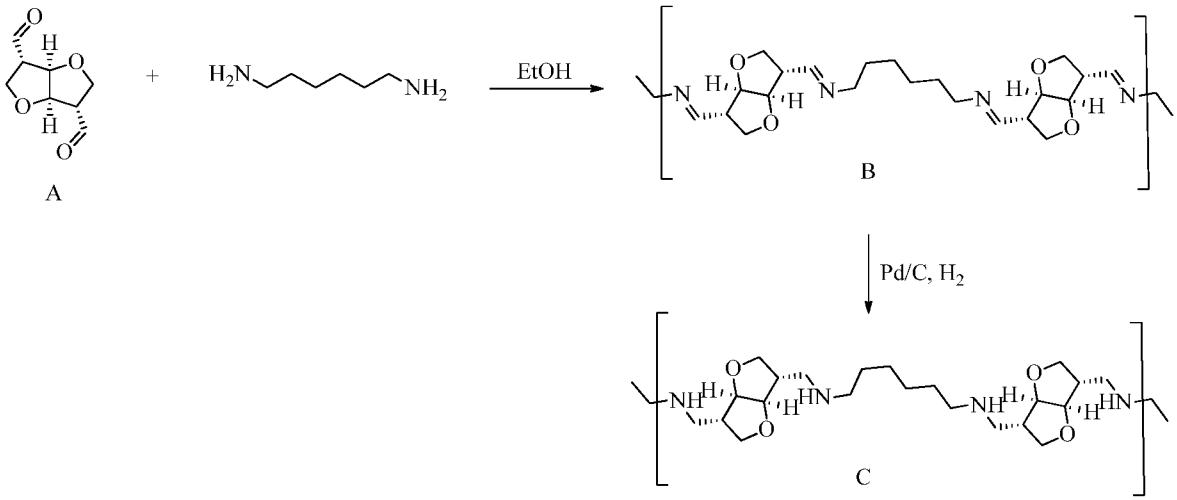
[0048] Example 2: Synthesis of diiminohexane-isomannide **B** and diaminohexane **C** oligomers from isomannide-3,6-dicarbaldehyde **A** and 1,6-diaminohexane.



A B C

Experimental: A single neck, 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 25 mg of isomannide-3,6-dicarbaldehyde (0.147 mmol), 17 mg of 1,6-hexanediamine and 2 mL of ethanol. The mixture was stirred overnight at room temperature. After this time, excess solvent was removed via rotary evaporation (40°C, 35 torr), and then placed under high vacuum for 2 days, affording 40.9 mg of a pale yellow wax. This material was re-dissolved in 2 mL of ethanol and placed into a 50 cc Parr reactor vessel. 25 mg of 10% Pd/C was then added, the vessel sealed, and charged with 250 psi H_2. The mixture was stirred for 3 hours at room temperature, after which the vessel vented, and catalyst filtered over a CELITE™ pad. The filtrate was then inspissated under reduced pressure, furnishing 39.8 mg a transparent solid material, presumably target C. Approximately 5 mg of this was dissolved in 0.750 mL of d^6-DMSO and analyzed by NMR. ^1H NMR revealed broad signals with expected chemical shifts, though integrations proved to be too cumbrous to interpret. ^{13}C NMR provided sharp, definable signals (400 MHz, d^6-DMSO) δ (ppm) 90.2, 87.1, 69.8, 50.0, 46.2, 42.6, 31.4, 30.3, 26.8, 26.1.

[0049] Example 3. Synthesis of diiminohexane-isoidide **B** and diaminohexane **C** oligomers from isoidide-3,6-dicarbaldehyde **A** and 1,6-diaminohexane.

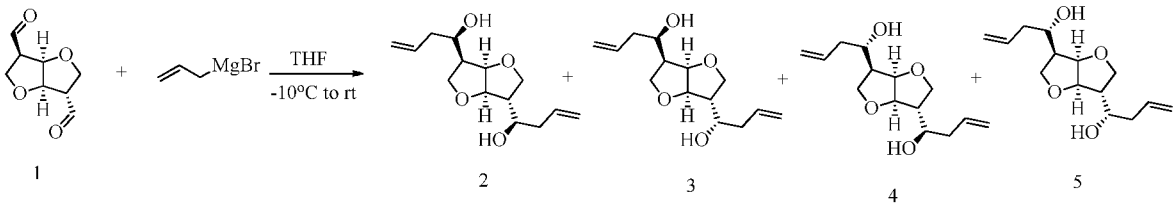


Experimental: A single neck, 10 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 25 mg of isoidide-3,6-dicarbaldehyde (0.147 mmol), 17 mg of 1,6-hexanediamine and 2 mL of ethanol. The mixture was stirred overnight at room temperature. After this time, excess solvent was removed via rotary evaporation (40°C, 35 torr), and then placed under high vacuum for 2 days, affording 40.2 mg of a pale yellow wax. This material was re-dissolved in 2 mL of ethanol and placed into a 50 cc Parr reactor vessel. 25 mg of 10% Pd/C was then added, the vessel sealed, and charged with 200 psi H_2. The mixture was stirred for 2 hours at room temperature, after which the vessel vented, and catalyst filtered over a CELITE™ pad. The filtrate was then decocted under reduced pressure, furnishing 40.6 mg a transparent solid material, presumably target

C. Approximately 5 mg of this was dissolved in 0.750 mL of d^6-DMSO and analyzed by NMR. ^1H NMR revealed broad signals with expected chemical shifts, though integrations proved to be too cumbrous to interpret. ^{13}C NMR provided sharp, definable signals (400 MHz, d^6-DMSO) δ (ppm) 89.6, 86.8, 69.2, 50.5, 46.7, 42.2, 31.0, 30.9, 25.8, 25.4.

B. Diallyl-glycol variants of isohexide-3,6-dicarbaldehydes

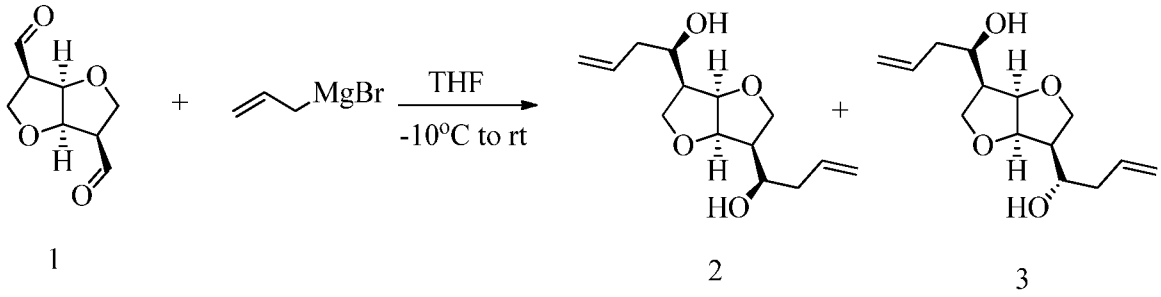
[0050] Example 1.: Synthesis of (1R,1'R)-1,1'-((3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(but-3-en-1-ol) **1**, (1S,1'R)-1,1'-((3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(but-3-en-1-ol) **2**, (1R,1'S)-1,1'-((3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(but-3-en-1-ol) **3**, (1S,1'S)-1,1'-((3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(but-3-en-1-ol),**4**.



1 2 3 4 5

Experimental: A single neck, oven dried, 10 mL round bottomed flask equipped with a ¼" PTFE magnetic stir bar was charged with 50 mg of **A** (0.294 mmol) and 2 mL of anhydrous tetrahydrofuran (THF). The neck was then stoppered with a rubber septum and an argon gas inlet attached. The flask was then immersed in an ice/brine bath (-10°C), and, while vigorously stirring and under an argon blanket, 588 µL of allylmagnesium bromide (1 M in diethyl ether, 0.588 mmol) was added dropwise over 10 minutes. The brine was then removed and mixture continued stirring overnight at room temperature overnight. After this time, the solution was diluted with 10 mL of methylene chloride and 10 mL of water and resultant biphasic mixture transferred to a separatory funnel. The bottom layer was partitioned, and aqueous layers extracted twice with 5 mL volumes of methylene chloride. The organic layers were then combined, dried with anhydrous sodium sulfate and concentrated under reduced pressure, producing 51 mg of isomers **2-5** as a pale yellow, loose oil (68% of theoretical). ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.96 (m, 2H) 5.14 (m, 2H), 5.11 (m, 2H), 3.91 (m, 2H), 3.60-3.54 (m, 6H), 3.30 (m, 2H), 2.26-2.24 (m, 4H), 2.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm) 135.2, 135.1, 117.1, 116.9, 85.1, 84.3, 66.1, 65.9, 64.6, 64.5, 52.3, 52.1, 40.4, 40.2.

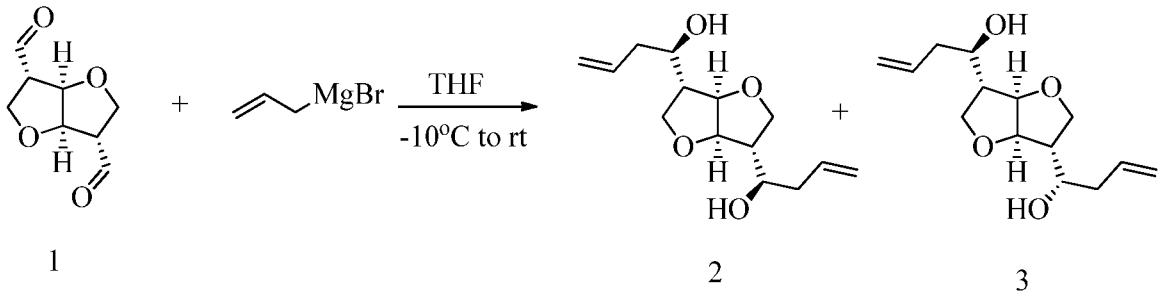
[0051] Example 2.: Synthesis of (1R,1'R)-1,1'-((3S,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(but-3-en-1-ol) **2**, and (1S,1'R)-1,1'-((3S,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(but-3-en-1-ol) **3**.



1 2 3

Experimental: A single neck, oven dried, 10 mL round bottomed flask equipped with a ¼" PTFE magnetic stir bar was charged with 50 mg of **A** (0.294 mmol) and 2 mL of anhydrous THF. The neck was then stoppered with a rubber septum and an argon gas inlet attached. The flask was then immersed in an ice/brine bath (-10°C), and, while vigorously stirring and under an argon blanket, 588 µL of allyl-magnesium bromide (1 M in diethyl ether, 0.588 mmol) was added dropwise over 10 minutes. The brine was then removed and mixture continued stirring overnight at room temperature overnight. After this time, the solution was diluted with 10 mL of methylene chloride and 10 mL of water and resultant biphasic mixture transferred to a separatory funnel. The bottom layer was partitioned, and aqueous layers extracted twice with 5 mL volumes of methylene chloride. The organic layers were then combined, dried with anhydrous sodium sulfate and concentrated under reduced pressure, producing 56 mg of isomers **2** and **3** as yellow, loose oil (75% of theoretical). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.92 (m, 2H) 5.12 (m, 2H), 5.09 (m, 2H), 3.87 (m, 2H), 3.60-3.54 (m, 6H), 3.30 (m, 2H), 2.24-2.19 (m, 4H), 2.05 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm) 135.0, 117.4, 84.9, 65.6, 64.8, 51.7, 40.8.

[0052] Example 3.: Synthesis of (1R,1'R)-1,1'-((3R,3aR,6R,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(but-3-en-1-ol) **2**, (1S,1'R)-1,1'-((3R,3aR,6R,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)bis(but-3-en-1-ol) **3**.



1 2 3

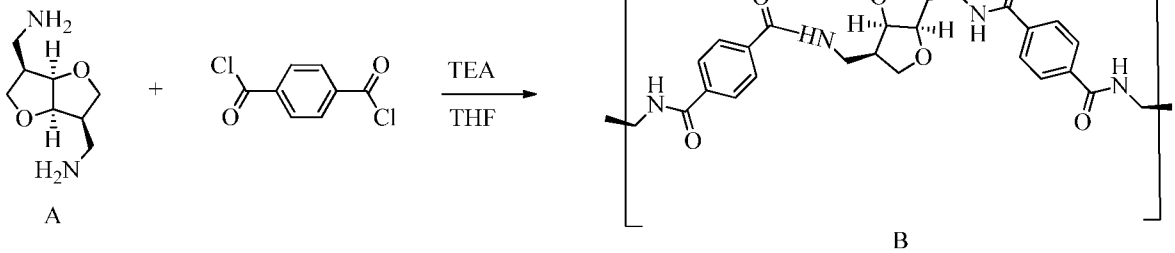
Experimental: A single neck, oven dried, 10 mL round bottomed flask equipped with a ¼" PTFE magnetic stir bar was charged with 50 mg of **A** (0.294 mmol) and 2 mL of anhydrous THF. The neck was then stoppered with a rubber septum and an argon gas inlet attached. The flask was then immersed in an ice/brine bath (-10°C), and, while vigorously stirring and under an argon blanket, 588

μL of allylmagnesium bromide (1 M in diethyl ether, 0.588 mmol) was added dropwise over 10 minutes. The brine was then removed and mixture continued stirring overnight at room temperature overnight. After this time, the solution was diluted with 10 mL of methylene chloride and 10 mL of water and resultant biphasic mixture transferred to a separatory funnel. The bottom layer was partitioned, and aqueous layers extracted twice with 5 mL volumes of methylene chloride. The organic layers were then combined, dried with anhydrous sodium sulfate and concentrated under reduced pressure, producing 58 mg of isomers **2** and **3** as a colorless, loose oil (78% of theoretical). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 5.89 (m, 2H) 5.09 (m, 2H), 5.06 (m, 2H), 3.89 (m, 2H), 3.58-3.53 (m, 6H), 3.27 (m, 2H), 2.22-2.18 (m, 4H), 2.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm) 134.7, 116.9, 84.7, 65.9, 64.4, 51.3, 40.5.

III. – Derivatives of Isohexide-3,6-Dimethanamines

[0053] The following examples illustrate the preparation of certain terephthalic-isohexide amine polymers derived from isohexide-3,6-dimethanamine.

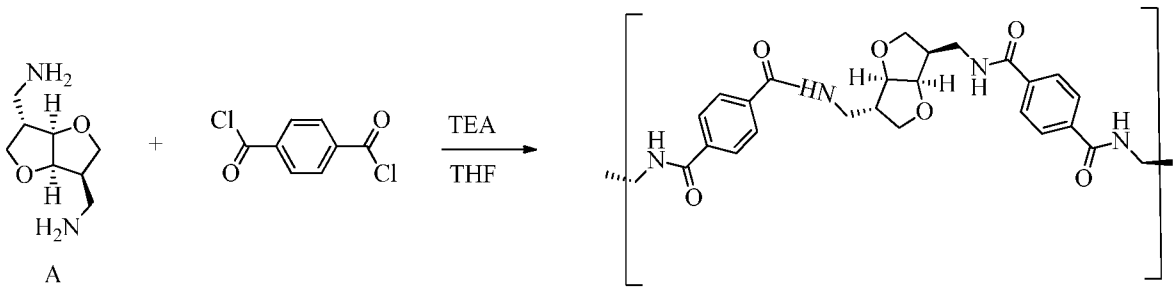
[0054] Example 1.: Synthesis of isomannide-3,6-dimethanamine-terephthalate polyamide **B** from isomannide-3,6-dimethamine **A**.



A B

Experimental: A 5 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 10 mg of **A** (0.0581 mmol), 11.8 mg of terephthaloyl chloride (dissolved in 1 mL of tetrahydrofuran (THF)), 17 μL of triethylamine ($N(CH_2CH_3)_3$, commonly abbreviated as Et_3N or TEA), and 1 mL of THF. Once stirring began, an almost immediate silky, yellowish precipitate formed. Stirring was halted after 1 hour and the stringy yellow solid filtered then dried. The structure is presumed to be the polyamide **B**.

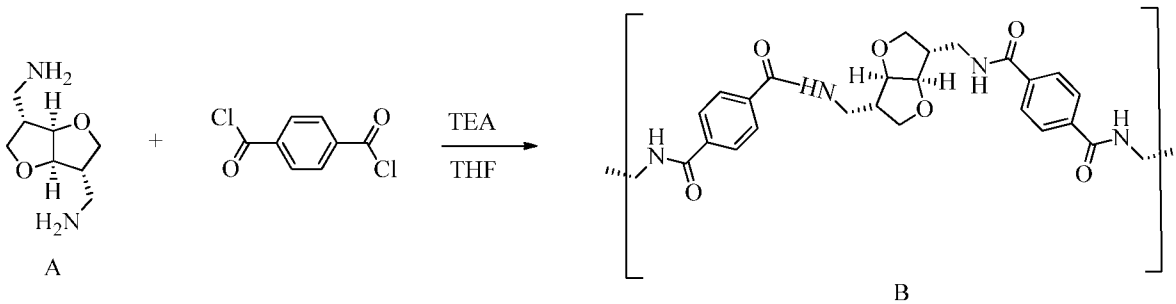
[0055] Example 2.: Synthesis of isosorbide-3,6-dimethanamine-terephthalate polyamide **B** from isosorbide-3,6-dimethanamine **A**.



A B

Experimental: A 5 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 10 mg of **A** (0.0581 mmol), 11.8 mg of terephthaloyl chloride (dissolved in 1 mL of THF), 17 µL of triethylamine, and 1 mL of THF. Once stirring began, an almost immediate white, silky precipitate formed. Stirring was halted after 1 hour and the stringy white solid filtered then dried. The structure is presumed to be the polyamide **B**.

[0056] Example 3.: Synthesis of isoidide-3,6-dimethanamine-terephthalate polyamide **B** from isoidide-3,6-dimethanamine **A**.



A B

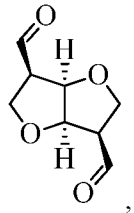
Experimental: A 5 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 10 mg of **A** (0.0581 mmol), 11.8 mg of terephthaloyl chloride (dissolved in 1 mL of THF), 17 µL of triethylamine, and 1 mL of THF. Once stirring began, an almost immediate chalk-colored, silky precipitate formed. Stirring was halted after 1 hour and the stringy, chalky-white solid filtered then dried. The structure is presumed to be the polyamide **B**.

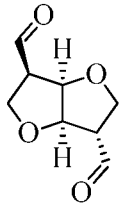
[0057] Although the present invention has been described generally and by way of examples, it is understood by those persons skilled in the art that the invention is not necessarily limited to the embodiments specifically disclosed, and that modifications and variations can be made without departing from the spirit and scope of the invention. Thus, unless changes otherwise depart from the scope of the invention as defined by the following claims, they should be construed as included herein.

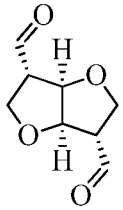
CLAIMS

We claim:

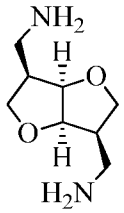
1. A method of making isohexide-3,6-dicarbaldehyde comprising: providing a reaction mixture containing an isohexide-3,6-dinitrile and an anhydrous, inert, organic solvent; contacting said isohexide-3,6-dinitrile with a reducing agent at a reaction temperature for a time sufficient to produce said isohexide-3,6-dicarbaldehyde.
2. The method according to claim 1, further comprising transforming an isohexide into said isohexide-3,6-dinitrile.
3. The method according to claim 2, wherein said isohexide is at least one of isomannide, isosorbide, and isoidide.
4. The method according to claim 1, wherein said inert organic solvent is a polar and aprotic solvent species.
5. The method according to claim 1, wherein said reducing agent is selected from the group consisting of: diisobutylaluminium hydride (DIBALH), sodium borohydride, and lithium aluminum hydride.
6. The method according to claim 1, further comprising contacting said isohexide-3,6-dicarbaldehyde with an aminating agent under reducing conditions to produce an isohexide-3,6-dimethanamine.
7. The method according to claim 6, wherein said aminating agent is selected from the group consisting of: $BnNH_2$, ammonia, and ammonium chloride.
8. The method according to claim 6, subjecting said aminating agent to a heterogeneous catalyst with H_2 gas to reduce to primary amines.
9. The method according to claim 1, wherein said reaction temperature is in a range from about -50°C to about -100°C.
10. The method according to claim 9, wherein said reaction temperature is about -60°C to about -90°C.
11. The method according to claim 1, wherein said inert organic solvent has a melting point below -90°C.
12. The method according to claim 1, wherein said inert organic solvent is at least one of toluene, methylene chloride, diethyl ether, and THF.
13. The method according to claim 1, wherein said the yields of isohexide-3,6-dicarbaldehydes are at least 47 mol.% conversion of said isohexide-3,6-dinitrile.
14. The method according to claim 6, wherein said the yields of isohexide-3,6-dimethanamines are at least 68 mol.% conversion of said isohexide-3,6-dicarbaldehyde.
15. The method according to claim 1, wherein said isohexide-3,6-dicarbaldehyde is at least one of:

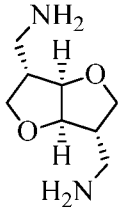
a) (3R,3aR,6R,6aR)-hexahydrofuro[3,2-b]furan-3,6-dicarbaldehyde:  ,

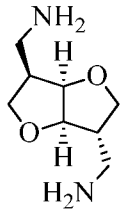
b) (3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-dicarbaldehyde:  , or

c) (3S,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-dicarbaldehyde:  .

16. The method according to claim 6, wherein said isohexide-3,6-dimethanamine is at least one of:

a) ((3R,3aR,6R,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)dimethanamine:  ,

b) ((3S,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)dimethanamine:  , or

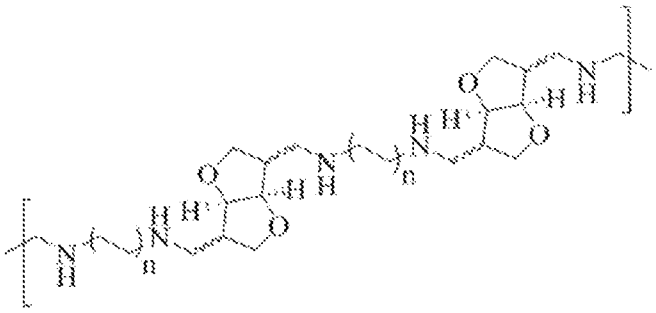
c) ((3R,3aR,6S,6aR)-hexahydrofuro[3,2-b]furan-3,6-diyl)dimethanamine:  .

17. A method of preparing an isohexide derivative compound of a isohexide-3,6-dicarbaldehyde comprising: reacting a mixture containing isohexide-3,6-dinitriles, and an inert organic solvent with a reducing agent at a reaction temperature between about -50°C to about -100°C; forming an isohexide-3,6-dicarbaldehyde; and transforming said isohexide-3,6-dicarbaldehyde into a bicyclic tetrahydrofuranic derivative compound.

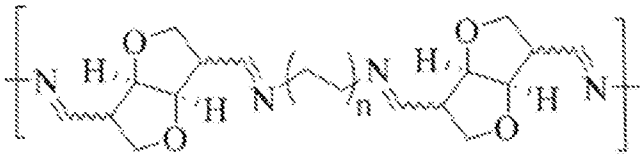
18. The method according to claim 17, wherein said transforming of said isohexide-3,6-dicarbaldehyde derivative compound further comprises: performing at least one of the following reactions: 1) reductive amination and polymerization, or 2) bis-allylation and glycolation.

19. The method according to claim 18, wherein said ioshexide derivative compound is either a) diaminohexane-isohexide, b) diiminohexane-isohexide polymer, or c) diallyl-glycols, with a general structure according to at least one of the following:

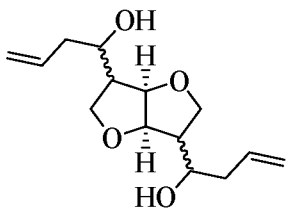
A)



B)



A3)



C)

20. The method according to claim 17, further comprising reductively aminating said isohexide-3,6-dicarbaldehyde to generate an isohexide-3,6-dimethanamine, and amidating said isohexide-3,6-dimethanamine to generate a polyamide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/65521

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/34; C07D 493/04 (2017.01)
CPC - C07D493/04; A61K31/34
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
CPC: C07D493/04; A61K31/34
IPC(8): A61K 31/34; C07D 493/04 (2017.01)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/469 (See Search Words Below)

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PATBASE: Full-text = AU BE BR CA CH CN DE DK EP ES FI FR GB IN JP KR SE TH TW US WO
Google: Scholar/Patents: isohexide-3,6-dicarbaldehyde dinitrile dicarbaldehyde diamine isosorbide dinitrile carbaldehyde nitrile lithium aluminum hydride ethyl acetate diamine reductive amination ammonia hydrogen gas polymerization isohexide-3,6-dimethanamine

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BROWN et al. 'Selective Reductions. IV. The Partial Reduction of Nitriles with Lithium Triethoxyaluminohydride-A Convenient Aldehyde Synthesis', Journal of the American Chemical Society, 1964, Vol. 86, pp. 1085-1089. pg 1086, Table 1; pg 1087, Col 1, para 4-5, Table III; pg 1088, Col 2, para 6 and para 9; pg 1089, Col 1, para 6	1-20
Y	WU et al. 'Isohexide Derivatives from Renewable Resources as Chiral Building Blocks', ChemSusChem, 2011, Vol 4, pp 599-603. pg. 599, Figure 1; pg 600, Scheme 2; pg 602, Col 2, para 2-3	1-20
Y	US 2010/0222611 A1 (TULCHINSKY et al.) 02 September 2010 (02.09.2010) para [0008];[0027];];[0052];[0061]	6-8, 16 ;20
Y	WO 2014/209595 A1 (ARCHER DANIELS MIDLAND COMPANY) 31 December 2014 (31.12.2014) pg 12, Example 4	19

☐ Further documents are listed in the continuation of Box C. ☐

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
31 January 2017	03 MAR 2017
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)