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(54) **Title:** DEHYDRATIVE CYCLIZATION OF PENTITOLS USING WATER-TOLERANT LEWIS ACID CATALYSTS UNDER MILD CONDITIONS AND DERIVATIVES

(57) **Abstract:** A catalytic process for the dehydrative cyclization of pentitols to synthesize anhydropentitols is described. Water-tolerant Lewis acids (in particular, metal triflates) are employed as catalysts to improve conversion and anhydropentitol selectivity at ultra-low catalyst loadings. The process can produce cyclic ether triols in high yields with concurrent complete pentitol conversion.



WO 2017/030684 A1

DEHYDRATIVE CYCLIZATION OF PENTITOLS USING WATER-TOLERANT LEWIS
ACID CATALYSTS UNDER MILD CONDITIONS AND DERIVATIVES

PRIORITY CLAIM

5 [0000] This Application claims benefit of priority of U.S. Provisional Application No. 62/205,340, filed August 14, 2015, the contents of which are incorporated herein by reference.

FIELD OF INVENTION

10 [0001] The present disclosure relates to cyclic tri-functional materials that can be useful as a precursor for various applications including polymers, surfactants, and plasticizers. In particular, the present invention pertains to tetrahydrofuran-based triols and methods by which these renewable molecular entities are produced.

15 BACKGROUND

[0002] Pentitols constitute a group of sugar alcohols that are derived from hydrogenation of naturally occurring carbohydrates, namely aldo- and ketopentoses. These molecular entities embody polytropic chemical platforms that can be used in various commercial applications, particularly in foodstuffs. Component individual sugar alcohols in the pentitol group include
20 xylitol, arabinitol, and ribitol (also known as adonitol). Of these three, xylitol has become the most familiar because of its prevalence and importance as a sugar substitute, low-calorie sweetener. Aside from xylitol, unfortunately the other pentitols have found heretofore limited commercial use. Xylitol derives from xylose, itself a monomeric unit of xylan (or hemicellulose) that is readily extracted from various woods (e.g., birch) and fibers (e.g.,
25 corncobs, corn stover, corn fiber). Although converted easily from arabinose, which also is a copious monomer in xylan, researchers have not found much use for arabinitol.

[0003] Xylan is estimated to be the second most common polysaccharide available in nature (Prakasham, *et al.*, Current Trends in Biotechnology and Pharmacy, 2009, 3, 8-36.) and, in turn, is facilely depolymerized via acid mediated hydrolysis, furnishing xylose that reduces to
30 xylitol via catalytic hydrogenation. In 2012, global production of xylitol was estimated at 275 MM lbs. with a bulk price tag of about \$2/lbs. (Chapter 13, "D-Xylitol Fermentative Production, Application and Commercialization", editors Silvio Silvério da Silva, Anuj Kumar Chandel. Springer 2012). Owing to its ubiquity as a sweetener in chewing gum, prodigious global expansion of xylitol production has remained steady for over a decade.
35 Currently, xylitol commands over 12% of the global polyols market, with an anticipated threefold increase (da Silva, *et. al.*), amounting to nearly 500 MM lbs. per annum by 2020.

[0004] Bulk xylitol generated worldwide derives predominantly from corncoobs (24% composition is xylan by weight dry biomass), corn stover (16.5% xylan) and birch tree fibers (the latter as a substantial waste-stream of the paper and pulping industry). The immense volume of corn cobs and stover generated each year from agricultural processing functions has spurred a renewed interest to reap greater value from such materials in addition to their traditional use as fertilizer for fields after the harvest. Moreover, xylitol production can open new opportunities for the use of this and other pentitols as a raw material in polymeric chemistry.

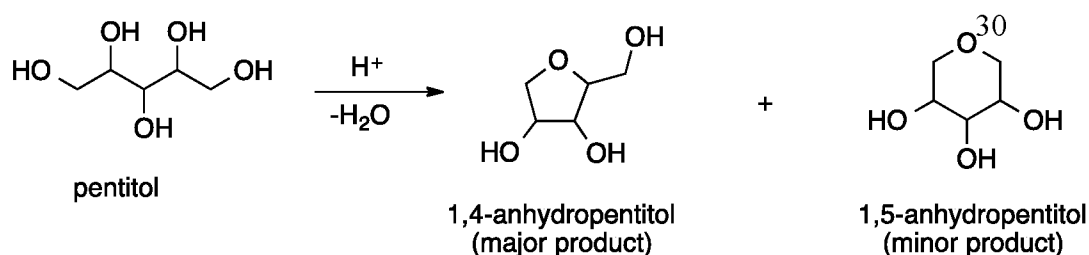
[0005] Researchers over the past decade have worked to develop efficient, environmentally or biologically benign pathways to convert 6 carbon polyols derived from hexoses such as glucose and fructose to less highly functionalized materials. The materials have included more stable bi-functional compounds, such as 2,5-furandicarboxylic acid (FDCA), levulinic acid, and 1,4:3,6-dianhydrohexitols. The potential to do likewise for pentitols opens an opportunity for a new class of precursor molecules for a variety of applications. A particular attractive feature of pentitol molecules is their ability to provide sequential chirality and poly-OH functionalities.

[0006] In view of the potential benefits that pentitol molecules can offer, dehydrated anhydropentitols can help advance synthesis of commercially valuable materials, such as surfactants, pre-polymers, plasticizers, pharmaceuticals, and dye precursors from renewable sources of pentoses. Hence, molecular entities derived from such materials would be novel and merit exploration.

[0007] Large industrial-scale uses of pentitol molecules, however, have been limited in part because of the “over-functionalization” of the molecules. For instance, catalytic dehydrative cyclization of xylitol to 1,4-anhydroxylitol is a transformation that has received relatively limited attention as a multifunctional tetrahydrofuran platform to date.

[0008] The few scientific citations that address the preparation of anhydropentitols have focused entirely on converting anhydroxylitol by means of Brønsted acid-catalyzed dehydration of the pentitol precursors, such as illustrated in Scheme A.

Scheme A.



(See for example: Skorupa, Eugenia *et al.*, *Carbohydrate Research*, 339(14), 2355-2362; 2004; J. Baddiley, J. G. Buchanan, B. Carss, and A.P Matthias, *J. Chem. Soc.*, 4583, 1956); Duclos, Alain *et al.*; *Synthesis*, (10), 1087-90; 1994; Chari, Ravi V. J. and Blattler, Walter A. PCT Int. Appl., 2001049698, 12 Jul 2001; J.F. Carson, and W.D. Maclay. *J. Amer. Chem. Soc.*, 1945, 67, 1808); Benattar, Andre *et al.*, PCT Int. Appl., 2014154958, 02 Oct. 2014.)

[0009] These kinds of reactions employ high molar amounts (e.g., $\geq 10\%$) of Brønsted acids, such as hydrochloric acid and phosphonic acid, at high temperatures for protracted times.

The reported yields of anhydropentitols are moderate to low and purification onerous. These associated features of the processes are problematic and contributes to limit efficient

production capacity. For instance, the need to use high acid concentrations can add to the costs of the synthesis. The inability to achieve higher yields of the target anhydroxylitol compounds (e.g., $< 50\%$) and supervening challenges for purification of the desire product can depress productivity and make such processes less attractive for industrial adoption or commercial application.

[0010] In view of the modest results, associated costs, and purification problems of current processes, a better method of preparing anhydropentitols that can more efficiently capture the industrial potential of these molecules is needed. A new process for making significant amounts of anhydropentitols from dehydrative cyclization of pentitols would be a welcome advance.

SUMMARY OF INVENTION

[0011] The present disclosure describes, in part, a method for preparing anhydropentitols from pentitol antecedents (i.e., xylitol, arabinitol (arabitol), and ribitol (adonitol)). The method involves contacting a C₅ sugar alcohol (pentitol) in the presence of a water-tolerant Lewis acid catalyst under reduced pressure at a temperature and time sufficient to effectuate dehydrative cyclization of the pentitol. Depending on the starting pentitol, the major cyclized products include 1,4-anhydroxylitol, 1,4-anhydroarabitol, 2,5-anhydroarabitol, or 1,4-anhydroribitol. The minor cyclized products include 1,5-anhydroxylitol, 1,5 anhydroarabitol and 1,5-anhydroribitol.

[0012] In another aspect, the present disclosure describes the use of water-tolerant Lewis acid catalysts for dehydrative cyclization of pentitols that can achieve conversion rate of at least 60% and anhydropentitol yields of greater than 50%. Alternatively, one can achieve a pentitol to anhydropentitol conversion rate of at least 80% and anhydropentitol yields greater than 70%, or a conversion rate of 100% and anhydropentitol yields of greater than 80%.

[0013] In another aspect, the present disclosure describes some derivative compounds that can be prepared from the anhydropentitols and synthesis protocols for their derivatization.

[0014] 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.

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BRIEF DESCRIPTION OF FIGURES

[0015] FIG. 1A, top, is a gas chromatograph (GC) trace of products from dehydrative cyclization of xylitol using 0.1 mol% Hf(OTf)₄ according to an embodiment of the present disclosure. FIG. 1B, bottom, is a GC trace of the xylitol precursor for purposes of comparison.

[0016] FIG. 2A, top, is a GC trace of products from dehydrative cyclization of ribitol using 0.1 mol% Hf(OTf)₄ according to an embodiment of the present disclosure. FIG. 1B, bottom, is a GC trace of the ribitol precursor for purposes of comparison.

[0017] FIG. 3A, top, is a GC trace of products from dehydrative cyclization of D-arabitol using 0.1 mol% Hf(OTf)₄ according to another embodiment. FIG. 3B, bottom, is a GC trace of the arabitol precursor for purposes of comparison.

DETAILED DESCRIPTION OF INVENTION

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Section I. Description

[0018] 1,4 and 1,5-anhydropentitols are a class of cyclic furanotriols that can have considerable value as renewable molecular entities. Derived from abundant carbohydrates, these molecules possess a structural similarity to other cyclic ether polyols that have exhibited favorable performances as surrogates for organic compounds that have been made traditionally from non-renewable petrochemical sources. As described in the Background section, the anhydropentitols are versatile chemical platforms that demand interest because of their intrinsic chiral tri-functionalities, which can permit chemists to expand significantly the frontiers of both existing and newly synthesized derivative compounds. In an effort to advance the technology for production of anhydropentitols, open the field of chemical research wider, and increase access to these molecules by means of improving yields and lowering production costs, we describe a new synthesis method.

30

A.

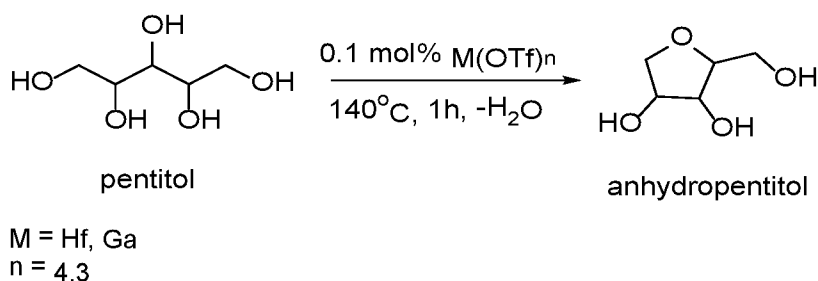
[0019] The present method of preparation enables one to augment the overall process efficiency while concurrently reducing the use of a reagent to moderate costs. In contrast to Brønsted acid catalyzed dehydrative cyclization of pentitols to anhydropentitols such as described in the Background section, which typically involve at least 10 mol.% catalyst

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loadings, the present method reduces the amount of catalyst that is needed and concomitantly furnishes higher yields of target anhydropentitols. The method can reduce substantially catalyst loadings by at least 50% relative to conventional practices. The method according to the present invention, requires only a minor amount of acid catalysts that in most cases is at least an order of magnitude less to achieve better yields of target anhydropentitols.

[0020] Scheme 1 delineates an embodiment of the synthetic method for metal triflate-catalyzed dehydration of pentitols to 1,4-anhydropentitols. In the present method, the pentitol can be at least one or more of the following: xylitol, arabinitol, ribitol (also called adonitol). As depicted the metal triflate is of hafnium or gallium, but other kinds of metals can also be employed.

Scheme 1. Scheme for Dehydrative Cyclization of Pentitols



[0021] Generally, the method encompasses performing a dehydrative cyclization with a pentitol in the presence of water-tolerant Lewis acid (“WTLA”) catalysts. As used herein, the term “water-tolerant” refers to the degree that a metal ion of a particular catalyst is resistant to being hydrolyzed by water. Metal triflates possess this remarkable trait, (e.g., see, *J. Am. Chem. Soc.* 1998, 120, 8287-8288, the content of which is incorporated herein by reference).

Such materials are receiving much attention in effectuating a multitude of chemical transformations, and are reviewed panoptically, in *Chem Rev*, 2002, 3641-3666, the contents of which are incorporated herein by reference.

[0022] According to the present invention, the water tolerant Lewis acid is a metal triflate.

For example, the water-tolerant Lewis acids may include one or more metal triflates selected from: transitional metals (e.g., scandium, hafnium, iron, copper, mercury, nickel, zinc, thallium), Lanthanide rare-earth metals (e.g., lanthanum, cerium, praseodymium, neodymium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, ytterbium, lutetium) and/or others (e.g., aluminum, gallium, indium, tin, bismuth). In certain preferred embodiments, the water-tolerant catalysts can be one or more metallic triflates of aluminum, tin, indium, hafnium, gallium, scandium, or bismuth.

[0023] The metal triflate catalyst can be present in an amount of at least 0.005 mol% relative to the amount of pentitol, but typically the amount is greater. When the catalyst is present in

an amount < 0.01 mol.%, the product mixture contains more unreacted pentitols. When amounts of catalyst loadings are about 0.01 mol% to about 0.1 mol%, the reaction manifests a greater degree of pentitol conversions and anhydropentitol yields. In an embodiment when the catalyst amount is about 0.01 mol.%, the method can exhibit pentitol conversions of $\geq$ 60%, and anhydropentitol yields $> 50\%$. The method can use catalysts in amounts of about 0.02 mol.% or 0.03 mol.% to about 0.05 mol% or 0.1 mol%. These embodiments manifested more efficacy with conversion of pentitols to corresponding anhydropentitols with yields of about 65% or greater. In certain embodiments, the catalysts load is about 0.04 mol.% or 0.05 mol.% to about 0.15 mol.% or 0.25 mol.%, manifesting good conversion rates and anhydropentitol yields of about $\geq 70\%$ or 75%.

[0024] Generally, higher catalyst loading levels result in greater pentitol conversion and higher anhydropentitol yields. In certain embodiments, the amount of Lewis acid catalyst load can be about 1 mol.% relative to the pentitol content. This produces complete (quantitative) conversion and $\geq 80\%$ yield of anhydropentitol. Nonetheless, for cost efficiency without sacrificing productivity, the amount of catalyst loading can be about 0.7 mol.% or 0.6 mol.%, more typically about 0.5 mol.% or 0.4 mol.%. The pentitol is nearly converted completely (>95 mol%) to a corresponding cyclized product with $\geq 75\%$ yield.

[0025] The reaction is executed at a reduced pressure of about 50 torr or less. Typically, the reaction pressure is about 5 torr or less (e.g., 1 torr, 2 torr or 3 torr).

[0026] The dehydration reaction is performed at a temperature in a range from about 120°C to about 180°C. Typically, the temperature range can be from about 125°C or 130°C to about 160°C or 170°C. In certain embodiments, the reaction temperature can be about 132°C or 135°C to about 140°C, 145°C or 150°C. For example, a reaction can be executed at a temperature up to about 160°C, and over an extended period, such as about 2-4 hours (120-240 minutes), or the reaction can be performed within about 1 hour. For example, the reaction time is in a range from about 30 minutes to about 180 minutes, typically about 60 to 120 minutes.

[0027] Depending on the starting material, from the dehydration reaction one can generate: 1,4-anhydroxylitol, 1,4-anhydroarabitol, 2,5-anhydroarabitol, and 1,4-anhydroribitol as the major cyclized products. One can achieve a yield at least 70% or 75% for 1,4-anhydropentitol or 2,5-anhydropentitol. Typically, the major product yield can be about 80% or greater (e.g., 85%, 87%, 90%, 92%, 95%, 97%). Minor cyclized products can include 1,5-anhydroxylitol, 1,5 anhydroarabitol and 1,5-anhydroribitol. As a minor product, the yield of 1,5-anhydropentitol is at most about 20%, but is typically less than about 10% or 15%.

Desirably the yield of minor product is less than about 5% (e.g., 4%, 3%).

[0028] The present method of preparation using WTLA-mediated dehydrative cyclization exhibits several advantages. For instance, the advantages include a) the complete conversion

of starting pentitols over short reaction times (e.g., ~1h); b) greater than 80% aggregate yields of anhydropentitols, of which about 65-95% is of the 1,4-anhydropentitol molecule; and c) relatively easy isolation of the 1,4-anhydropentitols by means of vacuum distillation.

5

B.

[0029] Once anhydropentitols are obtained, according to either the present dehydration method or another, one can prepare various derivative compounds from them. Some of these derivative compounds may be made according, for example, to the syntheses summarized in Schemes 2, 3, and 4, from anhydroarabitol, anhydroribitol, and anhydroxylitol respectively.

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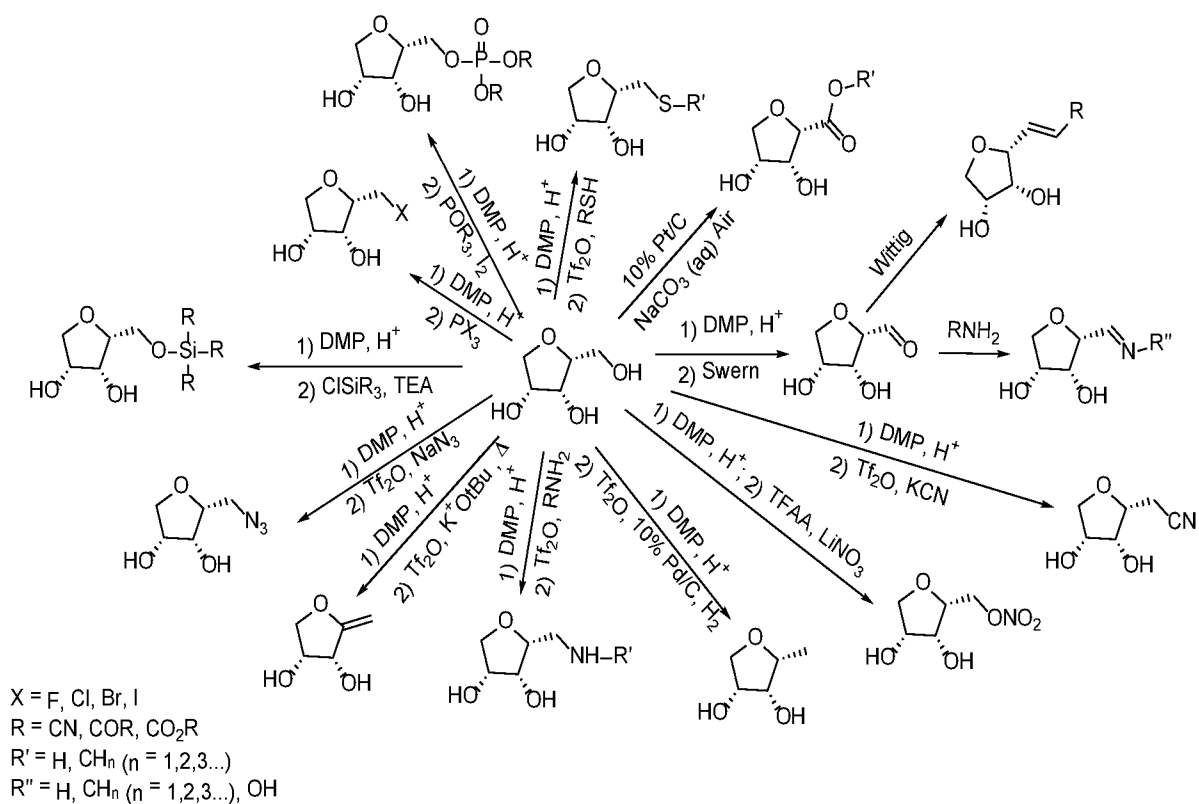
In Schemes 2 or 3, respectively, one may start with anhydroarabitol or anhydroribitol and perform certain synthesis reactions, shown in clockwise order, as:

1. *syn*-Glycol protection (acetonide), sulfonation, substitution (mercaptan nucleophile), deprotection;
2. Heyns oxidation, esterification;
- 15 3. *syn*-Glycol protection (acetonide), Swern oxidation, a) Wittig reaction; b) amination, deprotection;
4. Protection (acetonide), sulfonation, substitution (cyanide nucleophile), deprotection;
5. *syn*-Glycol protection, nitration, deprotection;
6. *syn*-Glycol protection, sulfonation, reduction, deprotection;
- 20 7. *syn*-Glycol protection, sulfonation, substitution (amine nucleophile), deprotection;
8. *syn*-Glycol protection, sulfonation, elimination;
9. *syn*-Glycol protection, sulfonation, substitution (azide nucleophile), deprotection;
10. *syn*-Glycol protection, silylation, deprotection;
11. *syn*-Glycol protection, substitution (halide nucleophile), deprotection; or
- 25 12. *syn*-Glycol protection, phosphonylation, deprotection.

In Scheme 4, for anhydroxylitol, the synthesis reactions performed, in clockwise order, include:

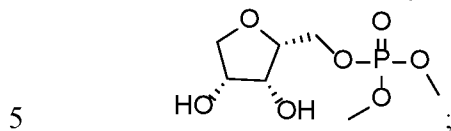
1. Heyns oxidation, esterification;
2. Swern oxidation, a) Wittig reaction, b) Amination
- 30 3. Sulfonation, hydrogenation; or
4. Direct silylation.

[0030] Scheme 2. – Derivative Compounds from Anhydroarabitol

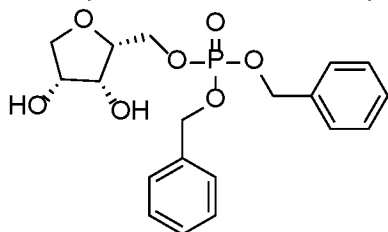


[0031] Examples of particular derivative compounds from anhydroarabitol may include:

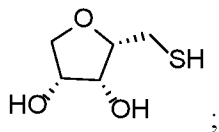
1. ((2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl dimethyl phosphate



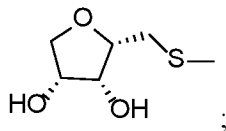
2. Dibenzyl (((2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl) phosphate



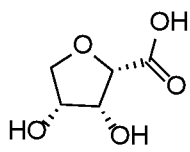
3. (2S,3R,4R)-2-(mercaptomethyl)tetrahydrofuran-3,4-diol



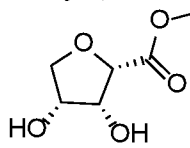
- 10 4. (2S,3R,4R)-2-((methylthio)methyl)tetrahydrofuran-3,4-diol



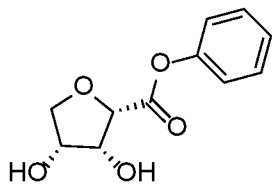
5. (2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carboxylic acid



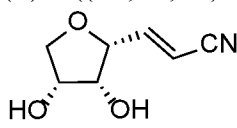
6. Methyl (2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carboxylate



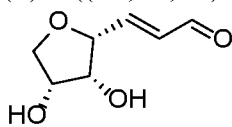
7. Phenyl (2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carboxylate



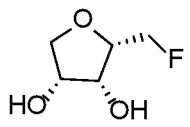
8. (E)-3-((2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)acrylonitrile



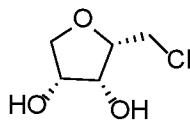
9. (E)-3-((2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)acrylaldehyde



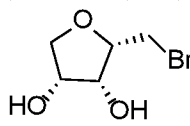
10. (2S,3R,4R)-2-(fluoromethyl)tetrahydrofuran-3,4-diol



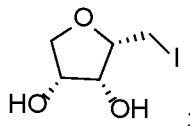
11. (2S,3R,4R)-2-(chloromethyl)tetrahydrofuran-3,4-diol



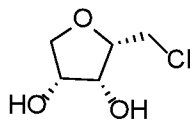
12. (2S,3R,4R)-2-(bromomethyl)tetrahydrofuran-3,4-diol



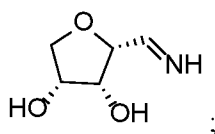
13. (2S,3R,4R)-2-(iodomethyl)tetrahydrofuran-3,4-diol



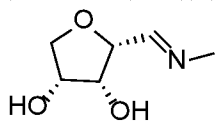
14. 2-((2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)acetonitrile



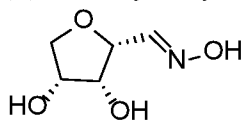
15. (2R,3R,4R)-2-(iminomethyl)tetrahydrofuran-3,4-diol



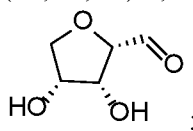
16. (2R,3R,4R)-2-((E)-(methylimino)methyl)tetrahydrofuran-3,4-diol



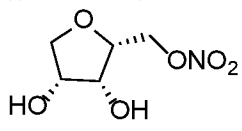
17. (E)-3,4-dihydroxytetrahydrofuran-2-carbaldehyde oxime



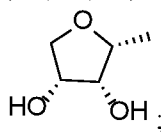
18. (2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carbaldehyde



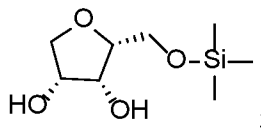
19. ((2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl nitrate



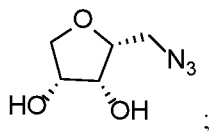
20. (2R,3R,4R)-2-methyltetrahydrofuran-3,4-diol



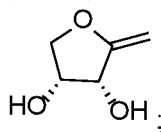
21. (2R,3R,4R)-2-(((trimethylsilyl)oxy)methyl)tetrahydrofuran-3,4-diol



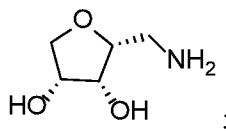
22. (2R,3R,4R)-2-(azidomethyl)tetrahydrofuran-3,4-diol



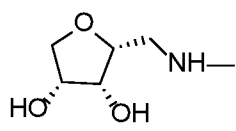
23. (3R,4R)-2-methylenetetrahydrofuran-3,4-diol



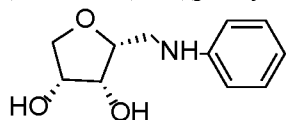
24. (2R,3R,4R)-2-(aminomethyl)tetrahydrofuran-3,4-diol



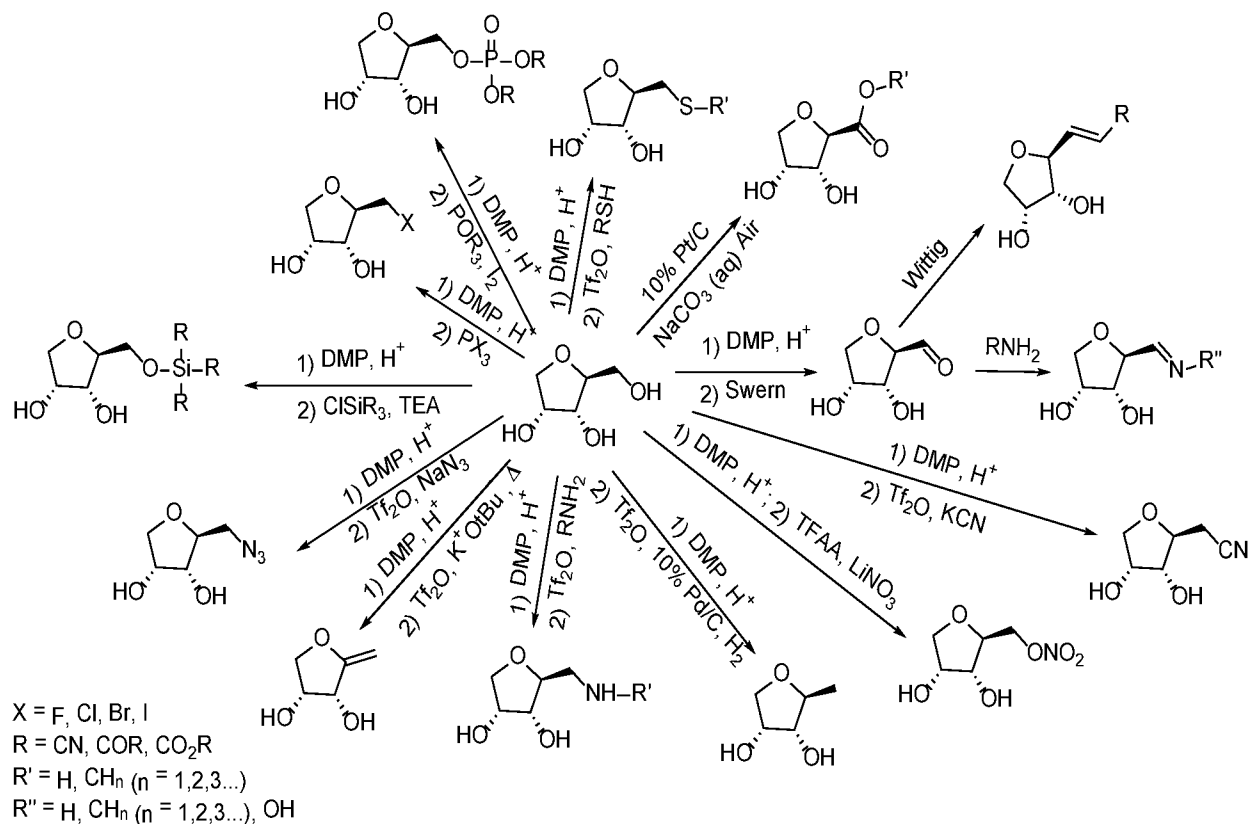
25. (2R,3R,4R)-2-((methylamino)methyl)tetrahydrofuran-3,4-diol



26. (2R,3R,4R)-2-((phenylamino)methyl)tetrahydrofuran-3,4-diol

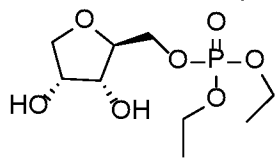


5 [0032] Scheme 3. – Derivative Compounds from Anhydrosorbitol

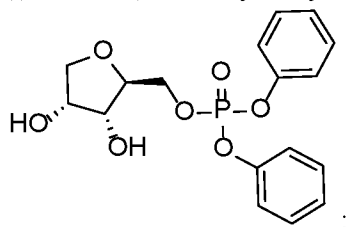


[0033] Examples of particular derivative compounds from anhydrosorbitol may include:

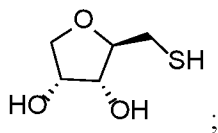
1. ((2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl diethyl phosphate



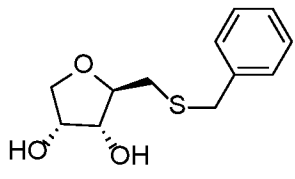
2. ((2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl diphenyl phosphate



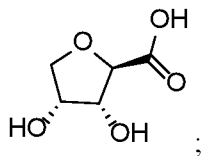
3. (2R,3R,4R)-2-(mercaptomethyl)tetrahydrofuran-3,4-diol



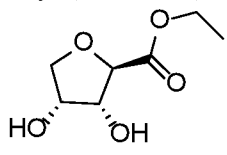
4. (2R,3R,4R)-2-((benzylthio)methyl)tetrahydrofuran-3,4-diol



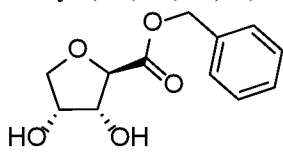
5. (2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carboxylic acid



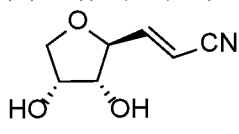
6. ethyl (2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carboxylate



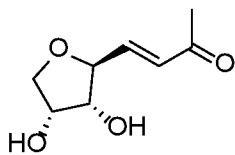
7. benzyl (2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carboxylate



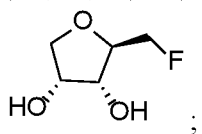
8. (E)-3-((2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)acrylonitrile



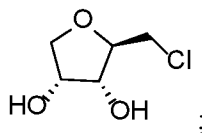
9. (E)-4-((2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)but-3-en-2-one



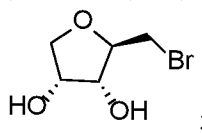
10. (2R,3R,4R)-2-(fluoromethyl)tetrahydrofuran-3,4-diol



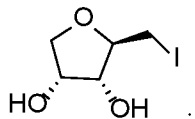
11. (2R,3R,4R)-2-(chloromethyl)tetrahydrofuran-3,4-diol



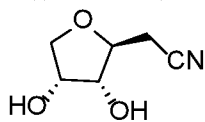
12. (2R,3R,4R)-2-(bromomethyl)tetrahydrofuran-3,4-diol



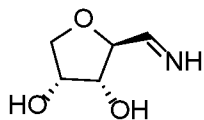
13. (2R,3R,4R)-2-(iodomethyl)tetrahydrofuran-3,4-diol



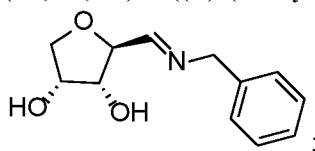
14. 2-((2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)acetonitrile



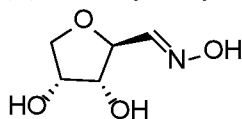
- 5 15. (2S,3R,4R)-2-(iminomethyl)tetrahydrofuran-3,4-diol



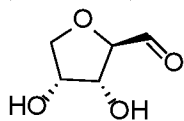
16. (2S,3R,4R)-2-((E)-(benzylimino)methyl)tetrahydrofuran-3,4-diol



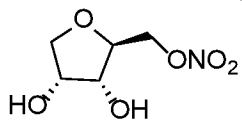
17. (E)-3,4-dihydroxytetrahydrofuran-2-carbaldehyde oxime



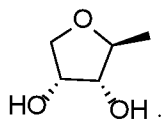
18. (2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carbaldehyde



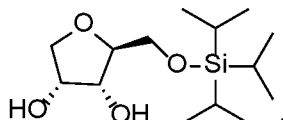
19. ((2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl nitrate



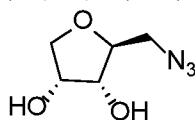
- 15 20. (2S,3R,4R)-2-methyltetrahydrofuran-3,4-diol



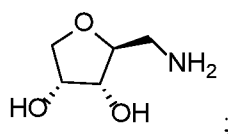
21. (2S,3R,4R)-2-(((triisopropylsilyl)oxy)methyl)tetrahydrofuran-3,4-diol



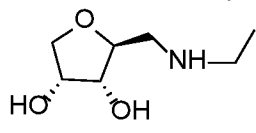
22. (2S,3R,4R)-2-(azidomethyl)tetrahydrofuran-3,4-diol



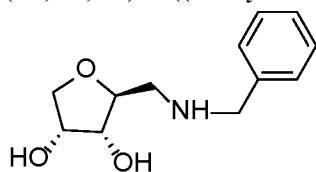
23. (2S,3R,4R)-2-(aminomethyl)tetrahydrofuran-3,4-diol



24. (2S,3R,4R)-2-((ethylamino)methyl)tetrahydrofuran-3,4-diol

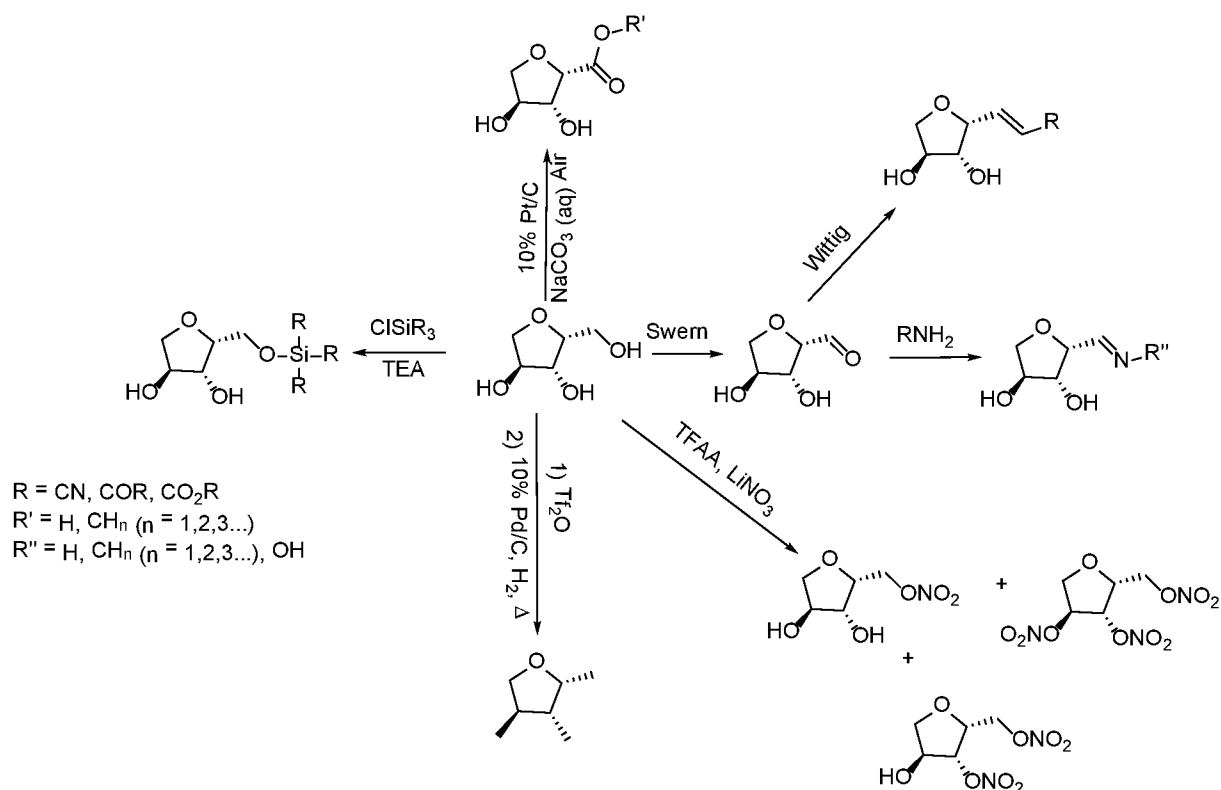


25. (2S,3R,4R)-2-((benzylamino)methyl)tetrahydrofuran-3,4-diol



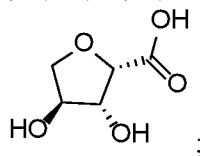
5

[0034] Scheme 4. – Derivative Compounds from Anhydroxylitol

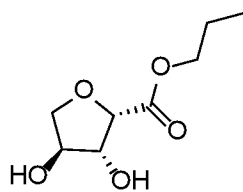


10 [0035] Examples of particular derivative compounds from anhydroxylitol may include:

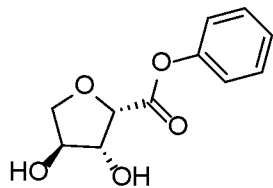
1. (2S,3R,4S)-3,4-dihydroxytetrahydrofuran-2-carboxylic acid



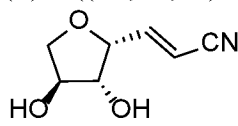
2. Propyl (2S,3R,4S)-3,4-dihydroxytetrahydrofuran-2-carboxylate



3. Phenyl (2S,3R,4S)-3,4-dihydroxytetrahydrofuran-2-carboxylate

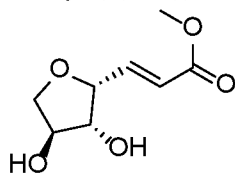


4. (E)-3-((2R,3R,4S)-3,4-dihydroxytetrahydrofuran-2-yl)acrylonitrile

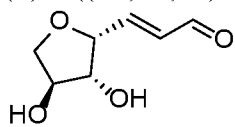


5

5. Methyl (E)-3-((2R,3R,4S)-3,4-dihydroxytetrahydrofuran-2-yl)acrylate

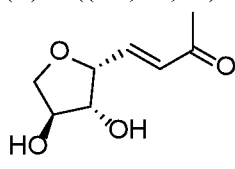


6. (E)-3-((2R,3R,4S)-3,4-dihydroxytetrahydrofuran-2-yl)acrylaldehyde

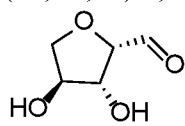


10

7. (E)-4-((2R,3R,4S)-3,4-dihydroxytetrahydrofuran-2-yl)but-3-en-2-one

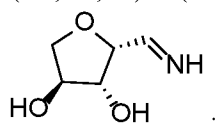


8. (2S,3R,4S)-3,4-dihydroxytetrahydrofuran-2-carbaldehyde

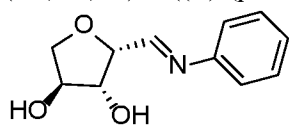


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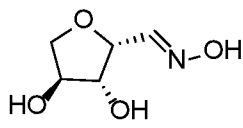
9. (2R,3R,4S)-2-(iminomethyl)tetrahydrofuran-3,4-diol



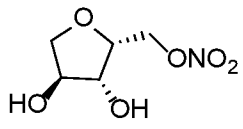
10. (2R,3R,4S)-2-((E)-(phenylimino)methyl)tetrahydrofuran-3,4-diol



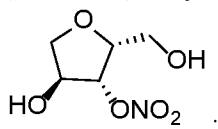
11. (E)-3,4-dihydroxytetrahydrofuran-2-carbaldehyde oxime



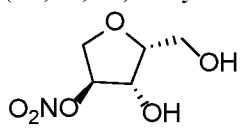
12. ((2R,3R,4S)-3,4-dihydroxytetrahydrofuran-2-yl)methyl nitrate



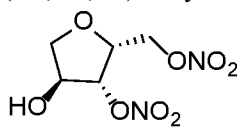
13. (2R,3R,4S)-4-hydroxy-2-(hydroxymethyl)tetrahydrofuran-3-yl nitrate



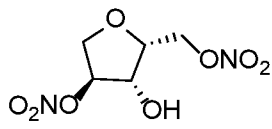
14. (3S,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl nitrate



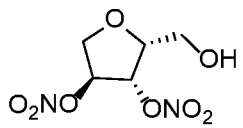
15. (2R,3R,4S)-4-hydroxy-2-((nitrooxy)methyl)tetrahydrofuran-3-yl nitrate



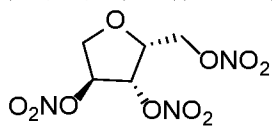
16. (3S,4S,5R)-4-hydroxy-5-((nitrooxy)methyl)tetrahydrofuran-3-yl nitrate



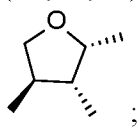
17. (2R,3S,4S)-2-(hydroxymethyl)tetrahydrofuran-3,4-diyl dinitrate



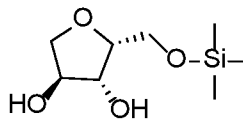
18. (2R,3S,4S)-2-((nitrooxy)methyl)tetrahydrofuran-3,4-diyl dinitrate



19. (2R,3R,4R)-2,3,4-trimethyltetrahydrofuran



20. (2R,3R,4S)-2-(((trimethylsilyl)oxy)methyl)tetrahydrofuran-3,4-diol



[0036] The scope of derivative compounds are not necessarily limited to the particular derivative compounds presented in the foregoing examples. Detailed descriptions of

synthesis protocols for some exemplar compounds are presented in the examples of Section II.

Section II. Examples

5 A. Representative Dehydration Method

[0037] In the following, we describe examples of preparations according to the present invention. In particular, the examples involve the use of low catalytic amounts of water-tolerant Lewis acid (WTLA) homogeneous catalysts hafnium triflate and gallium triflate to dehydrate and cyclize xylitol, arabinitol, and ribitol (also known as adonitol) to their
10 corresponding anhydropentitols. The pentitol starting materials can be readily obtained commercially as xylitol, arabinitol, and ribitol.

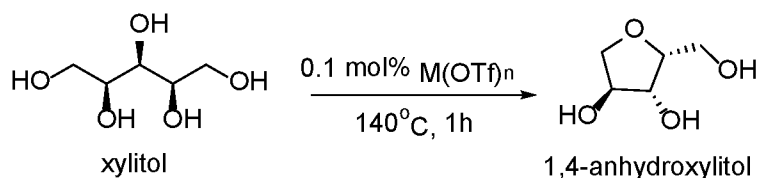
[0038] A significant finding from each of the examples was that the reactions favored one isomer over another. That is, the reaction produced a preponderance of the 1,4-substituted (~90%-95%) *vis a vis* the 1,5-substituted (~10%-5%) version of anhydropentitol. For sake of
15 illustration, the examples will focus on 1,4-substituted anhydropentitols.

[0039] A general experimental protocol for the dehydration of pentitols to anhydropentitols is as follows: A 25 mL round bottomed flask equipped with a PTFE coated magnetic stir bar was charged with 10.00 g of a pentitol (65.7 mmol) and 0.1 mol% of hafnium triflate (51 mg) or gallium triflate (34 mg). A short path condenser affixed to a vacuum line was then
20 attached to flask and while under vacuum (<1 torr), the mixture was heated to 140°C for 1 h in an oil bath. After this time, the vacuum was broken and contents cooled to room temperature. An aliquot was then removed and analyzed by GC.

[0040] A general description for the protocol used to purify 1,4-anhydropentitol is as follows: To a 100 mL, four-neck round bottomed flask was charged 50 g of aforementioned
25 anhydropentitol product mixture. The leftmost neck was affixed with a 30 cm Vigreux fractionating column, to the center neck an overhead stirrer with a Teflon blade, the rightmost neck a thermowell adapter threaded with a temperature probe, and the remaining frontal neck a ground glass adapter attached to a vacuum line. The flask was then enveloped in a spherical, soft-shell heating mantle and heated to 250-260°C (as indicated by the temp probe)
30 under reduced pressure (≤ 1 torr). Approximately 30-35 g of distillate was collected for each dehydrated pentitol. GC analysis of each manifested a lone salient signal indicating a highly pure 1,4-anhydropentitol (sans corresponding minor 1,5-anhydropentitol signal).

[0041] Example 1. Preparation of 1,4-anhydroxylitol from xylitol, catalyzed by a) hafnium triflate and b) gallium triflate.

35 Scheme Ex. 1.



M = Hf, Ga
n = 4,3

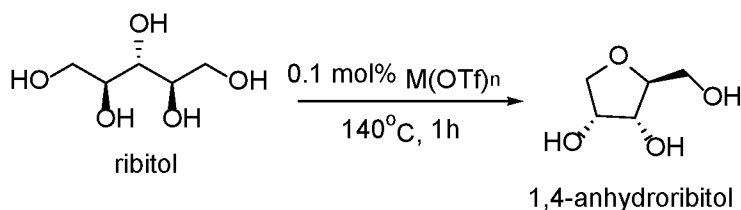
Table 1. GC results of a) hafnium triflate and b) gallium triflate mediated dehydrative cyclization of xylitol

Run	Catalyst	Catalyst Load (mol%)	Temp (°C)	% Xylitol Conversion @ 30 min	% Xylitol Conversion @ 60 min	% Yield of 1,4-anhydroxylitol
1	Ha(OTf) ₄	0.1	140	87	100	78
2	Ga(OTf) ₃	0.1	140	79	100	83

A gas chromatograph trace of the result of the reaction of xylitol using 0.1 mol% Hf(OTf)₄ is presented in Figure 1A.

[0042] Example 2. Preparation of 1,4-anhydroribitol from ribitol catalyzed by a) hafnium triflate and b) gallium triflate.

Scheme Ex. 2.



M = Hf, Ga
n = 4,3

Table 2. GC results from a) hafnium triflate and b) gallium triflate catalyzed dehydrative cyclization of ribitol

Run	Catalyst	Catalyst Load (mol%)	Temp (°C)	% Ribitol Conversion @ 30 min	% Ribitol Conversion @ 60 min	% Yield of 1,4-anhydroribitol
1	Ha(OTf) ₄	0.1	140	81	100	77
2	Ga(OTf) ₃	0.1	140	76	100	81

Figure 2A shows a gas chromatograph trace of the results of the reaction with of ribitol using 0.1 mol% Hf(OTf)₄.

[0043] Example 3. Preparation of 1,4-anhydroarabinitol from arabinitol catalyzed by a) hafnium triflate and b) gallium triflate. In another aspect, we describe the synthesis of derivative compounds from anhydropentitols. The particular compounds can be made according to the reactions depicted in Scheme 2, 3, or 4, and some of which are further expanded in the following examples.

Scheme Ex. 3.

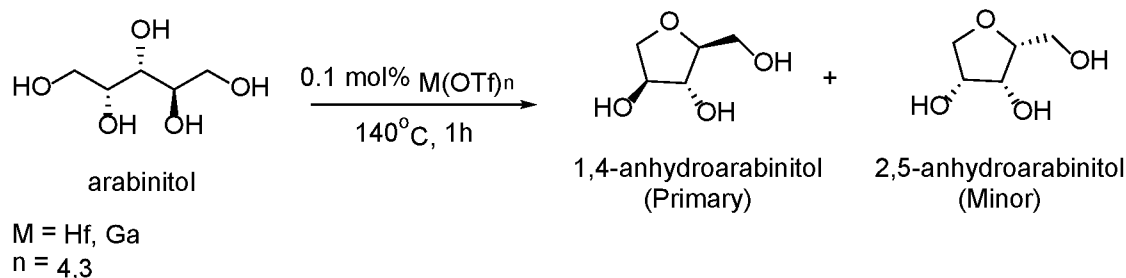


Table 3. GC results a) hafnium triflate and b) gallium triflate-mediated dehydrative cyclization of D-arabitol

Run	Catalyst	Catalyst Load (mol%)	Temp ($^\circ\text{C}$)	% Arabitol Conversion @ 30 min	% Arabitol Conversion @ 60 min	% Yield of 1,4-anhydroribitol, 2,5-anhydroarabitol*
1	$\text{Ha}(\text{OTf})_4$	0.1	140	75	100	74
2	$\text{Ga}(\text{OTf})_3$	0.1	140	77	100	78

* Cyclized isomers could not be separated

Figure 3A shows a gas chromatograph trace of the products from a reaction of arabitol using 0.1 mol% $\text{Hf}(\text{OTf})_4$.

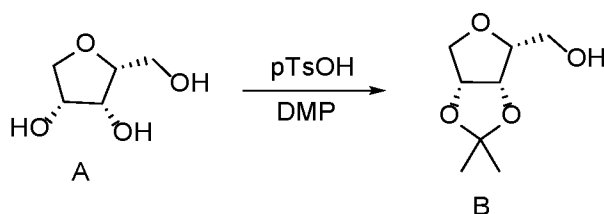
B. Representative Syntheses of Derivative Compounds

Anhydroarabitol

[0044]

Example 1.

General synthesis of ((3a*S*,4*R*,6a*R*)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-methanol, (B)



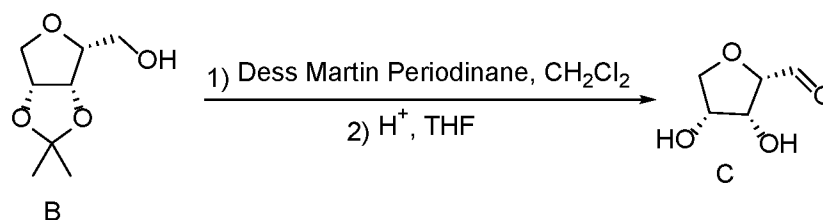
Experimental: A 50 mL round bottomed flask equipped with a PTFE magnetic stir bar was charged with 500 mg of anhydroarabitol A (3.72 mmol), 466 mg of 2,2-dimethoxypropane (DMP, 4.47 mmol), 20 mg of *p*-toluenesulfonic acid (*p*TsOH) and 20 mL of THF. The

homogeneous mixture was stirred overnight at room temperature. After this time, residual THF was evaporated under reduced pressure producing a light yellow oil that was purified by silica flash chromatography (cerium molybdate stain, gradient hexanes/ethyl acetate eluent), affording the 562 mg of the title compound as a clear oil (87%). ¹H NMR analysis (400 MHz, d⁶-DMSO) δ (ppm) 4.62 (m, 1H), 4.11 (m, 1H), 4.02 (m, 1H), 3.98 (m, 1H), 3.95 (m, 1H), 3.81 (m, 1H), 3.62 (m, 1H), 3.49 (m, 1H), 1.17 (s, 6H).

[0045]

Example 2.

10 Synthesis of (2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carbaldehyde, (C)



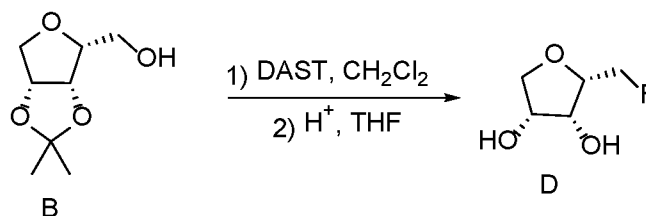
Experimental: A 25 mL round bottomed flask equipped with a PTFE magnetic stir bar was charged with 250 mg of B (1.43 mmol), 730 mg (1.72 mmol) of Dess Martin periodinane and 15 mL of dry methylene chloride. The resulting homogeneous mixture was stirred at room temperature overnight. After this time, the solution was poured directly on a prefabricated silica gel column, where flash chromatography (cerium molybdate stain) with a gradient hexanes/ethyl acetate eluent rendered a colorless oil that was then charged to a 10 mL round bottomed flask along with 5 mL of THF and 1 mL of concentrated HCl. The corresponding mixture was stirred for 1 hour, vestigial THF and HCl removed via rotary evaporation (40°C, 30 mmHg), and remaining oil dried under high vacuum overnight (0.5 mmHg), furnishing 161 mg of the title compound C (85%). ¹H NMR analysis (400 MHz, d⁶-DMSO) δ (ppm) 9.66 (d, J = 7.8 Hz), 4.72 (m, 1H), 4.44 (m, 2H), 4.21 (m, 1H), 4.10 (m, 1H), 3.99 (m, 1H), 3.81 (m, 1H), 3.55 (m, 1H).

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[0046]

Example 3.

Synthesis of (2S,3R,4R)-2-(fluoromethyl)tetrahydrofuran-3,4-diol, (D)

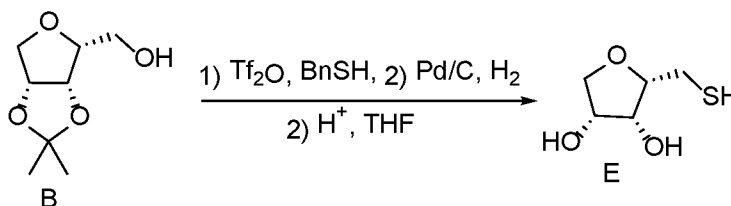


Experimental: A 25 mL round bottomed flask equipped with a PTFE magnetic stir bar was charged with 250 mg of B (1.43 mmol) and 10 mL of dry methylene chloride. The flask was stoppered with a rubber septum and while vigorously stirring, 277 mg of N,N-diethylaminosulfur trifluoride (DAST, 1.72 mmol) was added dropwise via syringe over 15 minutes. After addition, the mixture continued stirring overnight. After this time, the solution was poured directly on a prefabricated silica gel column, where flash chromatography (cerium molybdate stain) with a gradient hexanes/ethyl acetate eluent rendered a colorless oil that was then charged to a 10 mL round bottomed flask along with 5 mL of THF and 1 mL of concentrated HCl. The corresponding mixture was stirred for 1 hour, vestigial THF and HCl removed via rotary evaporation (40°C, 30 mmHg), and remaining oil dried under high vacuum overnight (0.5 mmHg), furnishing 135 mg of the title compound D (69%). ¹H NMR analysis (400 MHz, d⁶-DMSO) δ (ppm) 4.66 (m, 1H), 4.60 (m, 2H), 4.51 (m, 1H), 4.44 (m, 1H), 4.39 (m, 1H), 4.12 (m, 1H), 3.96 (m, 1H), 3.80 (m, 1H), 3.66 (m, 1H).

[0047]

Example 4.

Synthesis of (2S,3R,4R)-2-(mercaptomethyl)tetrahydrofuran-3,4-diol, (E)



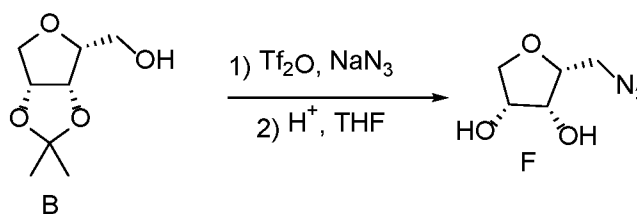
Experimental: A 25 mL round bottomed flask equipped with a PTFE magnetic stir bar was charged with 250 mg of B (1.43 mmol) and 10 mL of dry methylene chloride. The flask was stoppered with a rubber septum then immersed in a saturated dry ice/acetone solution (-78°C). While stirring, 444 of triflic anhydride (Tf_2O , 1.57 mmol) was added dropwise via syringe over 10 min. After this time, the flask was withdrawn from the cold acetone solution and stirred at room temperature for 1 hour. A 195 mg quantity of benzyl mercaptan (1.57 mmol) was then added and the resultant yellow solution stirred for an additional 4 hours. The mixture was then transferred to a 75 cc SS316 Parr vessel, charged with 500 mg of 5% Pd/C , diluted with 25 mL of methylene chloride, and sealed. The vessel was then pressurized with sufficient hydrogen gas to reach 1000 psi and agitated overhead at 875 rpm for 2 hours. Afterwards, the Pd/C catalyst was filtered and the residual solution poured directly on a prefabricated silica gel column, where flash chromatography (cerium molybdate stain) with a gradient hexanes/ethyl acetate eluent rendered a pale yellow oil that was then charged to a 10 mL round bottomed flask along with 5 mL of THF and 1 mL of concentrated HCl. The

corresponding mixture was stirred for 1 hour, vestigial THF and HCl removed via rotary evaporation (40°C, 30 mmHg), and remaining yellow oil dried under high vacuum overnight (0.5 mmHg), furnishing 156 mg of the title compound E (73%). ¹H NMR analysis (400 MHz, d⁶-DMSO) δ (ppm) 4.65 (m, 1H), 4.58 (m, 2H), 4.40 (m, 1H), 4.05 (m, 1H), 4.00 (m, 1H), 3.92 (m, 1H), 3.80 (m, 1H), 2.81 (m, 1H), 2.44 (m, 1H), 1.7 (m, 1H).

[0048]

Example 5.

Synthesis of (2R,3R,4R)-2-(azidomethyl)tetrahydrofuran-3,4-diol, F



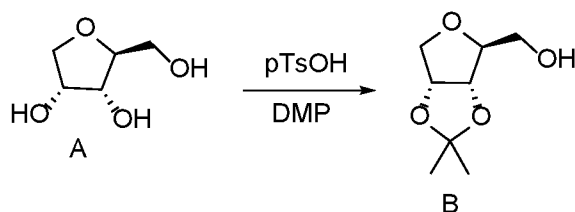
Experimental: A 25 mL round bottomed flask equipped with a PTFE magnetic stir bar was charged with 250 mg of B (1.43 mmol) and 10 mL of dry tetrahydrofuran. The flask was stoppered with a rubber septum then immersed in a saturated dry ice/acetone solution (-78°C). While stirring, 444 of triflic anhydride (Tf₂O, 1.57 mmol) was added dropwise via syringe over 10 min. After this time, the flask was withdrawn from the cold acetone solution and stirred at room temperature for 1 hour. A 186 mg lot of sodium azide (2.86 mmol) was then added and resulting mixture continued to stirred overnight. Afterwards, the residual solution poured directly on a prefabricated silica gel column, where flash chromatography (cerium molybdate stain) with a gradient hexanes/ethyl acetate eluent rendered a colorless oil that was then charged to a 10 mL round bottomed flask along with 5 mL of THF and 1 mL of concentrated HCl. The corresponding mixture was stirred for 1 hour, vestigial THF and HCl removed via rotary evaporation (40°C, 30 mmHg), and remaining loose, translucent oil dried under high vacuum overnight (0.5 mmHg), furnishing 149 mg of the title compound E (65%). ¹H NMR analysis (400 MHz, d⁶-DMSO) δ (ppm) 4.60 (m, 1H), 4.52 (m, 2H), 4.36 (m, 1H), 4.02 (m, 1H), 4.00 (m, 1H), 3.82 (m, 1H), 3.66 (m, 1H), 1.54 (m, 1H), 1.50 (m, 1H).

Anhydroribitol

[0049]

Example 1.

General synthesis of ((3aS,4S,6aR)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-methanol, (B)

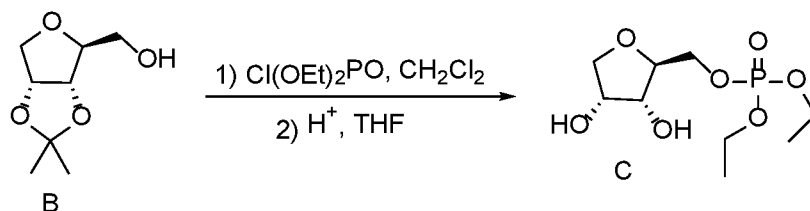


Experimental: A 50 mL round bottomed flask equipped with a PTFE magnetic stir bar was charged with 500 mg of anhydrosorbitol A (3.72 mmol), 466 mg of 2,2-dimethoxypropane (DMP, 4.47 mmol), 20 mg of p-toluenesulfonic acid (pTSA) and 20 mL of THF. The homogeneous mixture was stirred overnight at room temperature. After this time, residual THF was evaporated under reduced pressure producing a colorless oil that was purified by silica flash chromatography (cerium molybdate stain, gradient hexanes/ethyl acetate eluent), affording the 542 mg of the title compound as a clear oil (84%). ¹H NMR analysis (400 MHz, d⁶-DMSO) δ (ppm) 4.64 (m, 1H), 4.11 (m, 1H), 4.02 (m, 1H), 3.98 (m, 1H), 3.97 (m, 1H), 3.81 (m, 1H), 3.62 (m, 1H), 3.49 (m, 1H), 1.18 (s, 6H).

[0050]

Example 2.

Synthesis of ((2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl diethyl phosphate, (C)

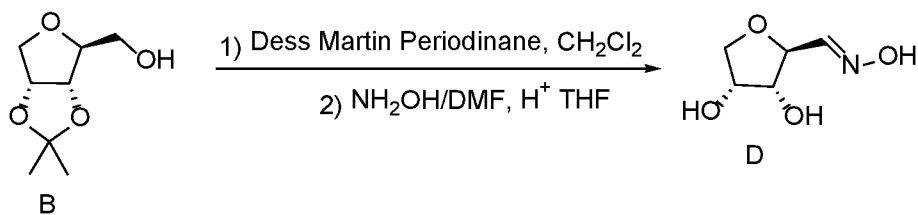


Experimental: A 25 mL round bottomed flask equipped with a PTFE magnetic stir bar was charged with 200 mg of B (1.15 mmol) and 10 mL of dry methylene chloride. The flask was then stoppered with a rubber septum and, while vigorously stirring, 257 mg of chlorotriethylphosphate (1.49 mmol) was added dropwise via syringe over 10 minutes. After this time, the solution was poured directly on a prefabricated silica gel column, where flash chromatography (cerium molybdate stain) with a gradient hexanes/ethyl acetate eluent rendered a colorless oil that was then charged to a 10 mL round bottomed flask along with 5 mL of THF and 1 mL of concentrated HCl. The corresponding mixture was stirred for 1 hour, vestigial THF and HCl removed via rotary evaporation (40°C, 30 mmHg), and remaining oil dried under high vacuum overnight (0.5 mmHg), furnishing 185 mg of the title compound C (59%). ¹H NMR analysis (400 MHz, d⁶-DMSO) δ (ppm) 4.59 (m, 1H), 4.54 (m, 1H), 4.44 (m, 2H), 4.40 (m, 1H), 4.24 (m, 1H), 4.09-4.05 (m, 7H), 3.81 (m, 1H), 1.40 (t, J = 8.0 Hz, 6H).

[0051]

Example 3.

Synthesis of (E)-3,4-dihydroxytetrahydrofuran-2-carbaldehyde oxime, (D)



5

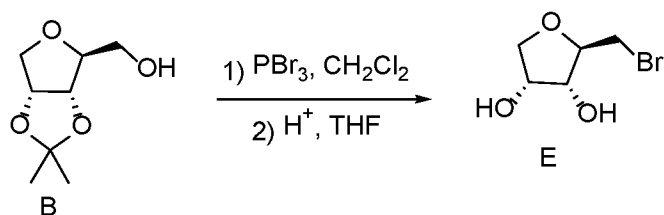
Experimental: A 25 mL round bottomed flask equipped with a PTFE magnetic stir bar was charged with 150 mg of B (0.861 mmol), 438 mg (1.03 mmol) Dess Martin periodinane and 10 mL of dry tetrahydrofuran. The resulting homogeneous mixture was stirred at room temperature overnight. After this time the flask was charged with 120 mg of hydroxylammonium chloride (1.72 mmol), 1 mL of dry trimethylamine, and 5 mL of dry dimethylformamide. The ensuing slurry was then stirred overnight. After this time, the solution was poured directly on a prefabricated silica gel column, where flash chromatography (cerium molybdate) with a gradient hexanes/ethyl acetate eluent rendered a colorless oil that was then charged to a 10 mL round bottomed flask along with 5 mL of THF and 1 mL of concentrated HCl. The corresponding mixture was stirred for 1 hour, vestigial THF and HCl removed via rotary evaporation (40°C, 30 mmHg), and remaining oil dried under high vacuum overnight (0.5 mmHg), furnishing 69 mg of the title compound D (54%).¹ H NMR analysis (400 MHz, d⁶-DMSO) δ (ppm) 10.99 (s, 1H), 6.86 (s, 1H), 4.41 (m, 1H), 4.37 (m, 1H), 4.00 (m, 1H), 3.96 (m, 1H), 3.92 (m, 1H), 3.81 (m, 1H), 3.70 (m, 1H).

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[0052]

Example 4.

Synthesis of (2R,3R,4R)-2-(bromomethyl)tetrahydrofuran-3,4-diol, (E)



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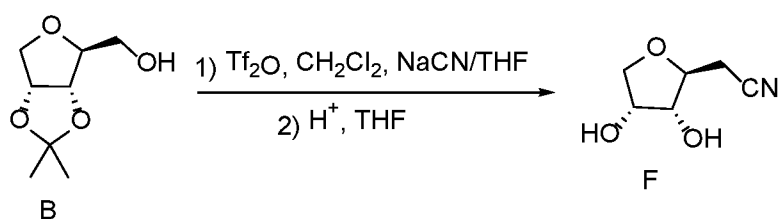
Experimental: A 25 mL round bottomed flask equipped with a PTFE magnetic stir bar was charged with 150 mg of B (0.861 mmol) and 10 mL of dry methylene chloride. The flask was

stoppered with a rubber septum, and while stirring, 350 mg (1.29 mmol) of phosphorus tribromide was added dropwise via syringe over 10 minutes. Once added, the resulting mixture continued stirring at room temperature overnight. After this time, the solution was poured directly on a prefabricated silica gel column, where flash chromatography (cerium molybdate) with a gradient hexanes/ethyl acetate eluent rendered a colorless oil that was then charged to a 10 mL round bottomed flask along with 5 mL of THF and 1 mL of concentrated HCl. The corresponding mixture was stirred for 1 hour, vestigial THF and HCl removed via rotary evaporation (40°C, 30 mmHg), and remaining oil dried under high vacuum overnight (0.5 mmHg), furnishing 77 mg of the title compound E (44%). ¹H NMR analysis (400 MHz, d⁶-DMSO) δ (ppm) 4.54 (m, 1H), 4.50 (m, 1H), 4.41 (m, 1H), 4.13 (m, 1H), 4.01 (m, 1H), 3.90 (m, 1H), 3.82 (m, 1H), 3.60 (m, 1H), 3.33 (m, 1H).

[0053]

Example 5.

Synthesis of 2-((2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)acetonitrile, (F)



Experimental: A 25 mL round bottomed flask equipped with a PTFE magnetic stir bar was charged with 150 mg of B (0.861 mmol) and 10 mL of dry tetrahydrofuran. The flask was stoppered with a rubber septum then immersed in a saturated dry ice/acetone solution (-78°C). While stirring, 291 of triflic anhydride (Tf_2O , 1.03 mmol) was added dropwise via syringe over 10 min. After this time, the flask was removed from the cold acetone solution and stirred at room temperature for 1 hour. An 84 mg measure of sodium cyanide (1.72 mmol) was then added and the resulting suspension stirred for an additional 24 hours. After this time, the solution was poured directly on a prefabricated silica gel column, where flash chromatography (cerium molybdate stain) with a gradient hexanes/ethyl acetate eluent rendered a colorless oil that was then charged to a 10 mL round bottomed flask along with 5 mL of THF and 1 mL of concentrated HCl. The corresponding mixture was stirred for 1 hour, vestigial THF and HCl removed via rotary evaporation (40°C, 30 mmHg), and remaining oil dried under high vacuum overnight (0.5 mmHg), furnishing 81 mg of the title compound F (66%). ¹H NMR analysis (400 MHz, d⁶-DMSO) δ (ppm) 4.54 (m, 1H), 4.50 (m,

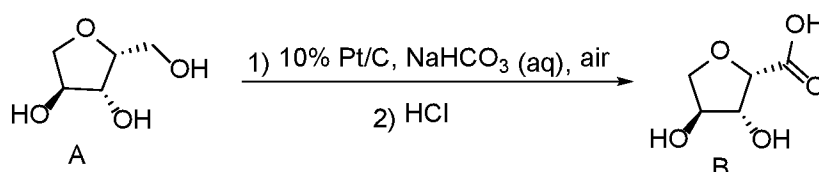
1H), 4.41 (m, 1H), 4.13 (m, 1H), 4.01 (m, 1H), 3.90 (m, 1H), 3.82 (m, 1H), 2.62 (m, 1H), 2.43 (m, 1H).

Anhydroxylitol

5 [0054]

Example 1.

Synthesis of (2S,3R,4S)-3,4-dihydroxytetrahydrofuran-2-carboxylic acid, B

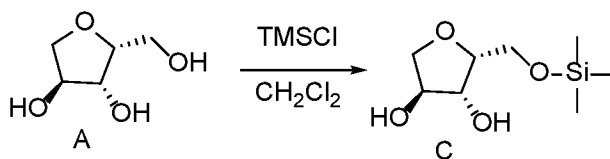


Experimental: A 250 mL three neck round bottomed flask equipped with a PTFE magnetic stir bar was charged with 1 g of A (7.45 mmol), 10 g of sodium bicarbonate, 5 g of 10% Pt/C and 150 mL of water. The necks were stoppered with rubber septa, with one pierced by a 12" needle air inlet, another a thermowell adapter, and the last a 12" needle air outlet. While stirring, the suspension was heated to 70°C with concomitant, vigorous air sparging for 10 hours. Amidst the reaction, 5 mL volumes of water were periodically added to the flask to compensate for that boiled off. After this time, solids were filtered (Pt/C catalyst and undissolved sodium bicarbonate) and concentrated HCl added dropwise until the pH of the solution was 5 (prodigious effervescence accompanied the addition). A single aqueous phase was observed. Water was evaporated under reduced pressure, affording a white solid that was crystallized in absolute ethanol, manifesting 396 mg (36%) of colorless needles. ¹H NMR (400 MHz, d⁶-DMSO) δ (ppm) 12.44 (s, 1H), 4.65 (m, 1H), 4.42 (m, 1H), 4.37 (m, 1H), 4.22 (m, 1H), 4.06 (m, 1H), 3.97 (m, 1H), 3.71 (m, 1H)

[0055]

Example 2.

25 Synthesis of (2R,3R,4S)-2-(((trimethylsilyl)oxy)methyl)tetrahydrofuran-3,4-diol, C



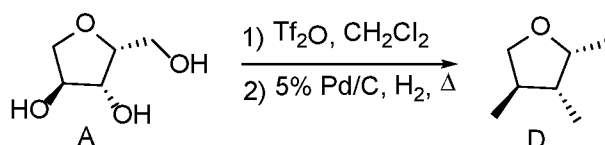
Experimental: Experimental: A 25 mL round bottomed flask equipped with a PTFE magnetic stir bar was charged with 500 mg of A (3.73 mmol) and 15 mL of methylene chloride. The flask was stoppered with a rubber septum, and immersed in a dry ice/acetone solution (-78°C). While stirring, trimethylsilyl chloride (4.47 mmol) was added via syringe over 10 minutes and stirred for 2 hours at this temperature. The flask was then removed from

the cold solution and stirring continued at room temperature for an additional 2 hours. After this time, the solution was poured on a pre-fabricated silica column, where flash chromatography (cerium molybdate stain) with a gradient hexanes/ethyl acetate eluent afforded 681 mg of the title compound C as loose, colorless oil (88%). ¹H NMR (400 MHz, d⁶-DMSO) δ (ppm) 4.55 (s, 1H), 4.51 (m, 1H), 4.42 (m, 1H), 4.35 (m, 1H), 4.07 (m, 1H), 4.02 (m, 1H), 3.98 (m, 1H), 3.75 (m, 1H), 3.70 (m, 1H), 0.17 (s, 9H).

[0056]

Example 3.

10 Synthesis of (2R,3R,4R)-2,3,4-trimethyltetrahydrofuran, D



Experimental: A 25 mL round bottomed flask equipped with a PTFE magnetic stir bar was charged with 500 mg of A (3.73 mmol) and 15 mL of methylene chloride. The flask was stoppered with a rubber septum, and immersed in a dry ice/acetone solution (-78°C). While stirring, 4.20 g of triflic anhydride (14.9 mmol) was added via syringe over 10 minutes. The flask was then removed from the cold solution and stirring continued at room temperature overnight. After this time, the dark solution was dried, viscous oil transferred to a 75 cc 316SS Parr vessel, 2 g of 5% Pd/C added, and 30 mL of absolute ethanol. The vessel was then sealed and pressurized with hydrogen gas until 1200 psi was achieved. While overhead agitating (1000 rpm), the heterogeneous solution was heated to 200°C for 8 hours. After this time, the solution was cooled to ambient, solids filtered, and residual clear, colorless solution dried under reduced pressure. The vestigial semi-solid was dissolved in a minimum amount of methylene chloride and charged to a pre-fabricated silica column, where flash chromatography (cerium molybdate stain) with a gradient hexanes/ethyl acetate eluent furnished the 201 mg of the title compound D as a loose oil (47%). ¹H NMR (400 MHz, d⁶-DMSO) δ (ppm) 3.80 (s, 1H), 3.71 (m, 1H), 3.47 (m, 1H), 1.92 (m, 1H), 1.77 (m, 1H), 1.16 (d, $J = 8.2$ Hz, 3H), 0.94 (d, $J = 8.0$ Hz, 3H), 0.84 (d, $J = 8.2$ Hz, 3H).

[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.

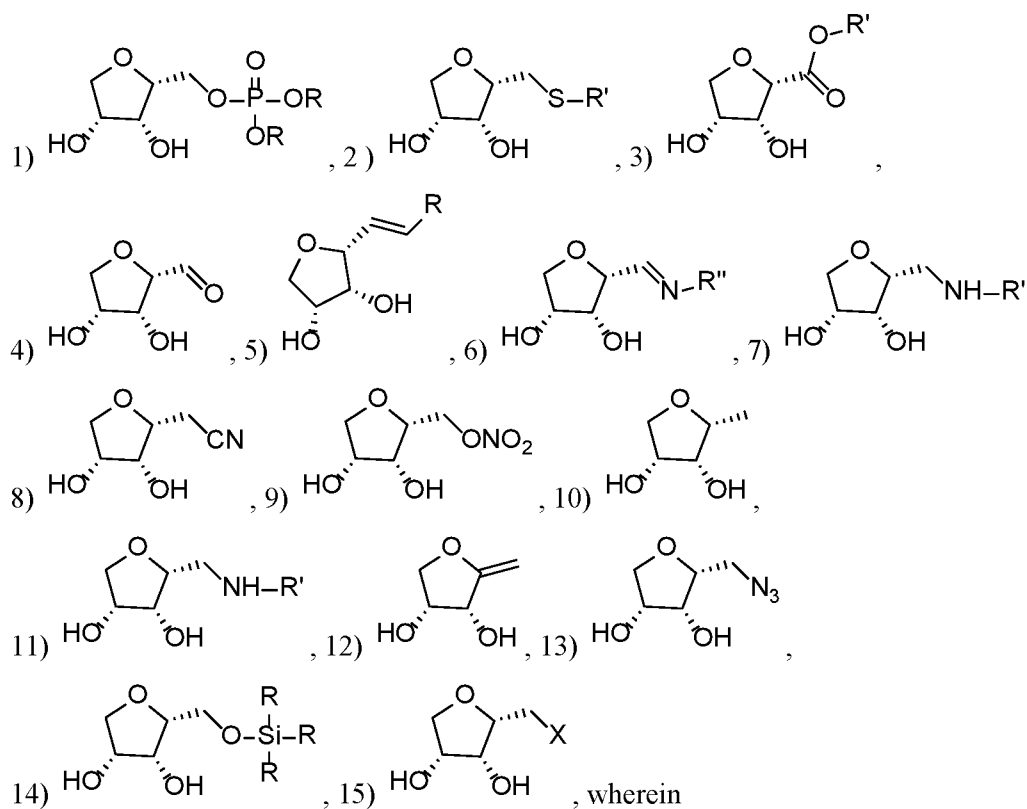
CLAIMS

We Claim:

1. A method for preparing anhydropentitols comprising: contacting a pentitol (C₅ sugar alcohol)
5 in the presence of a water-tolerant Lewis acid catalyst under reduced pressure at a temperature and time sufficient to effectuate dehydrative cyclization of said pentitol.
2. The method according to claim 1, wherein said pentitol is selected from the group consisting of: xylitol, arabinitol (arabitol) and ribitol (adonitol).
3. The method according to claim 1, wherein said water tolerant Lewis acid is a metal triflate,
10 selected from the group consisting of: scandium, hafnium, gallium, bismuth, mercury, iron, nickel, copper, zinc, aluminum, thallium, tin, indium, lanthanum, cerium, praseodymium, neodymium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, ytterbium, and lutetium.
4. The method according to claim 3, wherein said metal triflate is at least one of: hafnium,
15 gallium, scandium, and bismuth.
5. The method according to claim 1, wherein said dehydrative cyclization of said pentitol achieves a conversion rate of at least 60% and anhydropentitol yields of greater than 50%.
6. The method according to claim 1, wherein said dehydrative cyclization of said pentitol achieves a conversion rate of at least 80% and anhydropentitol yields of greater than 70%.
7. The method according to claim 1, wherein said dehydrative cyclization of said pentitol achieves a conversion rate of 100% and anhydropentitol yields of greater than 80%.
8. The method according to claim 1, wherein said reduced pressure is at about 50 torr or less.
9. The method according to claim 8, wherein said reduced pressure is about 5 torr or less.
10. The method according to claim 1, wherein said temperature is from about 120°C to about
25 180°C.
11. The method according to claim 10, wherein said temperature is in a range from about 130°C to about 150°C.
12. The method according to claim 1, wherein said time is in a range from about 30 minutes to about 240 minutes.
13. The method according to claim 12, wherein said time is about 60 minutes to about 180
30 minutes
14. The method according to claim 1, wherein when said pentitol is xylitol, then a major cyclized product is 1,4-anhydroxylitol, and a minor cyclized product is 1,5-anhydroxylitol.
15. The method according to claim 1, wherein when said pentitol is arabitol, then a major
35 cyclized product is either 1,4-anhydroarabitol or 2,5-anhydroarabitol, or both, and a minor cyclized product is 1,5 anhydroarabitol.

16. The method according to claim 1, wherein when said pentitol is ribitol, then a major cyclized product is 1,4-anhydribose, and a minor cyclized product is 1,5-anhydribose.
17. The method according to claim 1, wherein when said anhydropentitol is either 1,4-anhydropentitol or 2,5-anhydropentitol, then said anhydropentitol has a yield of at least 70%.
18. The method according to claim 1, wherein when said anhydropentitol is 1,5-anhydropentitol, then said anhydropentitol has a yield of at most about 20%.
19. A derivative compound of an anhydropentitol comprising a molecule according to at least one of the following:

A) from anhydroarabitol:



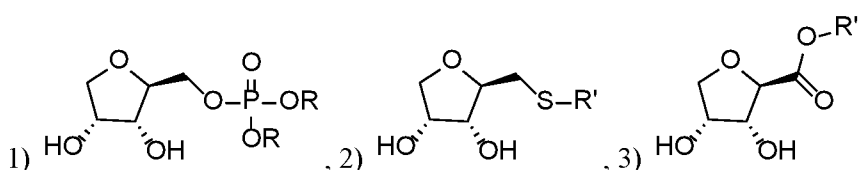
X = F, Cl, Br, I

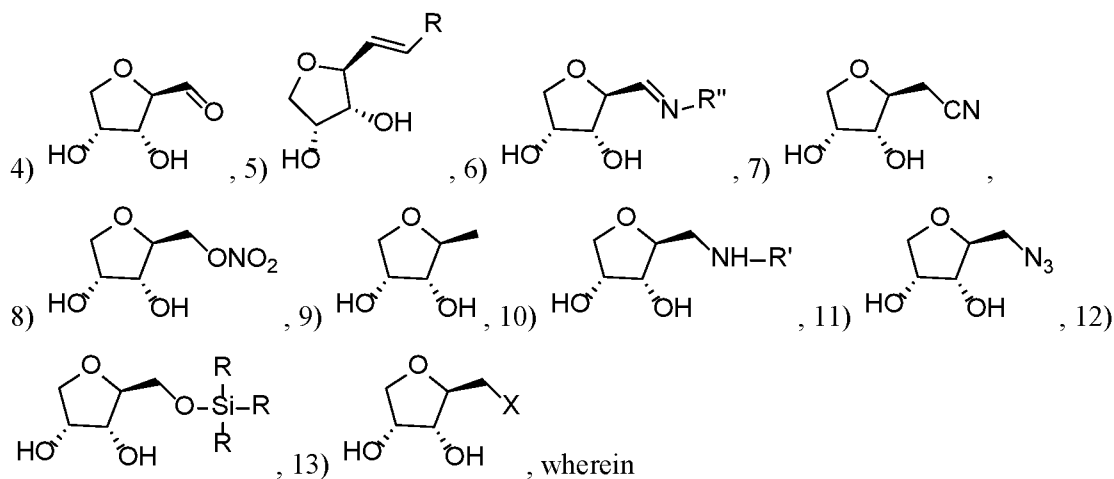
R = CN, COR, CO₂R

R' = H, CH_n (n = 1,2,3...)

R'' = H, CH_n (n = 1,2,3...), OH

B) from anhydribose:





X = F, Cl, Br, I

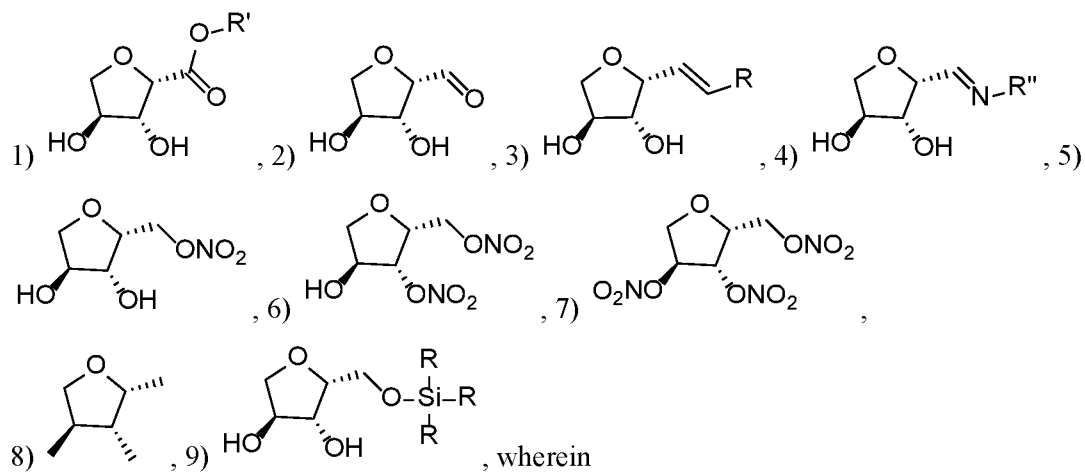
R = CN, COR, CO₂R

R' = H, CH_n (n = 1,2,3...)

R'' = H, CH_n (n = 1,2,3...), OH

5

C) from anhydroxylitol:



R = CN, COR, CO₂R

R' = H, CH_n (n = 1,2,3...)

R'' = H, CH_n (n = 1,2,3...), OH

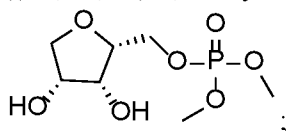
10

20. The derivative compound according to claim 19, wherein said molecule is at least one of the following:

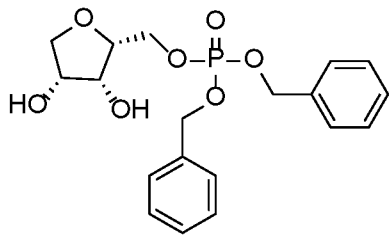
A) from anhydroarabitol:

15

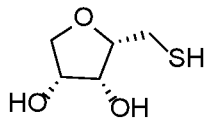
1 ((2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl dimethyl phosphate



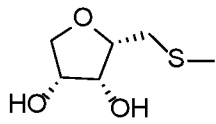
- 2 Dibenzyl (((2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl) phosphate



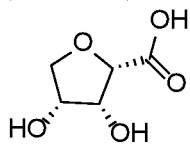
- 3 (2S,3R,4R)-2-(mercaptomethyl)tetrahydrofuran-3,4-diol



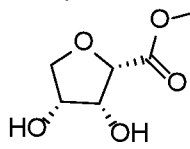
- 5 4 (2S,3R,4R)-2-((methylthio)methyl)tetrahydrofuran-3,4-diol



- 5 (2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carboxylic acid

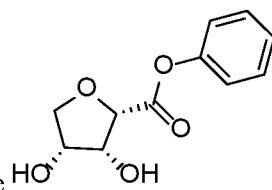


- 6 Methyl (2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carboxylate

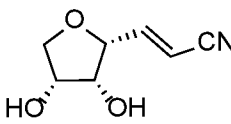


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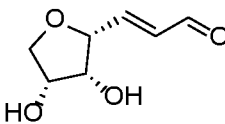
- 7 Phenyl (2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carboxylate



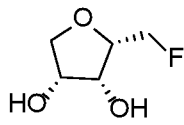
- 8 (E)-3-(((2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)acrylonitrile



- 9 (E)-3-(((2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)acrylaldehyde

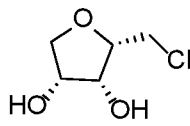


- 10 (2S,3R,4R)-2-(fluoromethyl)tetrahydrofuran-3,4-diol

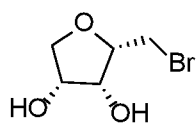


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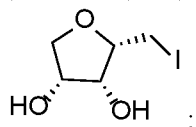
- 11 (2S,3R,4R)-2-(chloromethyl)tetrahydrofuran-3,4-diol



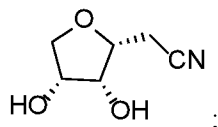
- 12 (2S,3R,4R)-2-(bromomethyl)tetrahydrofuran-3,4-diol



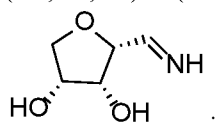
13 (2S,3R,4R)-2-(iodomethyl)tetrahydrofuran-3,4-diol



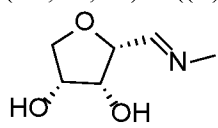
14 2-((2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)acetonitrile



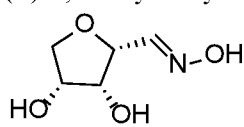
15 (2R,3R,4R)-2-(iminomethyl)tetrahydrofuran-3,4-diol



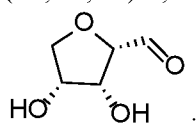
16 (2R,3R,4R)-2-((E)-(methylimino)methyl)tetrahydrofuran-3,4-diol



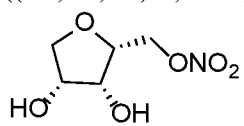
17 (E)-3,4-dihydroxytetrahydrofuran-2-carbaldehyde oxime



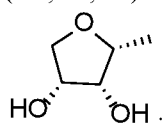
18 (2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carbaldehyde



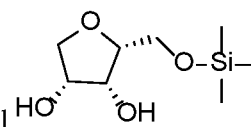
19 ((2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl nitrate



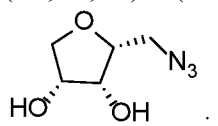
20 (2R,3R,4R)-2-methyltetrahydrofuran-3,4-diol



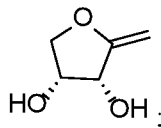
21 (2R,3R,4R)-2-(((trimethylsilyl)oxy)methyl)tetrahydrofuran-3,4-diol



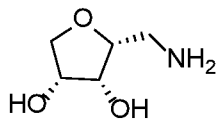
22 (2R,3R,4R)-2-(azidomethyl)tetrahydrofuran-3,4-diol



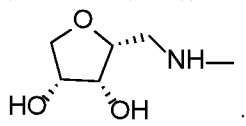
23 (3R,4R)-2-methylenetetrahydrofuran-3,4-diol



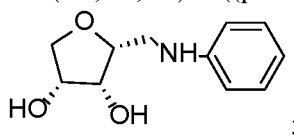
24 (2R,3R,4R)-2-(aminomethyl)tetrahydrofuran-3,4-diol



5 25 (2R,3R,4R)-2-((methylamino)methyl)tetrahydrofuran-3,4-diol

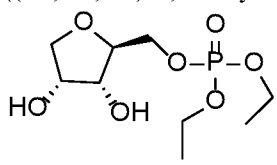


26 (2R,3R,4R)-2-((phenylamino)methyl)tetrahydrofuran-3,4-diol

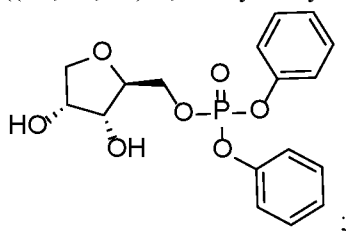


10 B) from anhydrosorbitol:

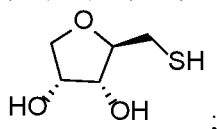
1. ((2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl diethyl phosphate



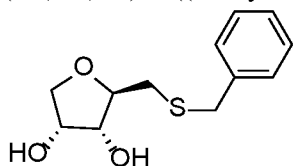
2. ((2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl diphenyl phosphate



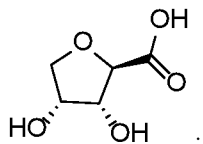
15 3. (2R,3R,4R)-2-(mercaptomethyl)tetrahydrofuran-3,4-diol



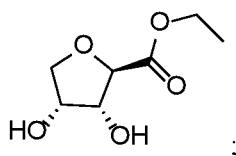
4. (2R,3R,4R)-2-((benzylthio)methyl)tetrahydrofuran-3,4-diol



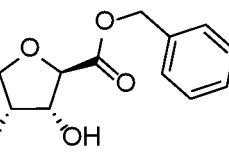
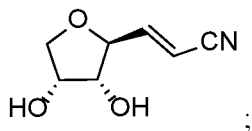
5. (2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carboxylic acid



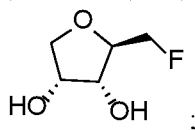
20 6. ethyl (2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carboxylate



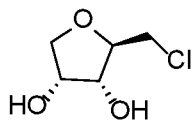
7. benzyl (2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carboxylate ;
 8. (E)-3-((2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)acrylonitrile



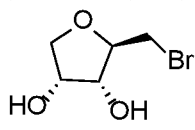
- 5 9. (E)-4-((2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)but-3-en-2-one ;
 10. (2R,3R,4R)-2-(fluoromethyl)tetrahydrofuran-3,4-diol



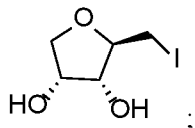
11. (2R,3R,4R)-2-(chloromethyl)tetrahydrofuran-3,4-diol



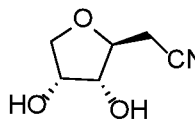
- 10 12. (2R,3R,4R)-2-(bromomethyl)tetrahydrofuran-3,4-diol



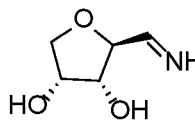
13. (2R,3R,4R)-2-(iodomethyl)tetrahydrofuran-3,4-diol



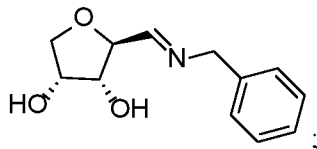
14. 2-((2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)acetonitrile



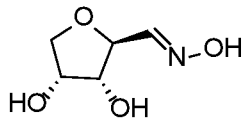
- 15 15. (2S,3R,4R)-2-(iminomethyl)tetrahydrofuran-3,4-diol



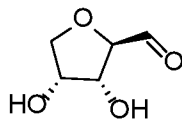
16. (2S,3R,4R)-2-((E)-(benzylimino)methyl)tetrahydrofuran-3,4-diol



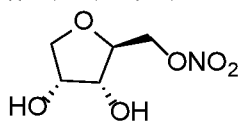
17. (E)-3,4-dihydroxytetrahydrofuran-2-carbaldehyde oxime



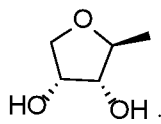
- 5 18. (2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-carbaldehyde



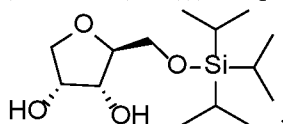
19. ((2S,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl nitrate



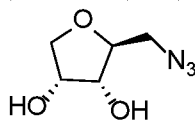
20. (2S,3R,4R)-2-methyltetrahydrofuran-3,4-diol



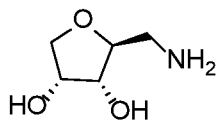
21. (2S,3R,4R)-2-(((triisopropylsilyl)oxy)methyl)tetrahydrofuran-3,4-diol



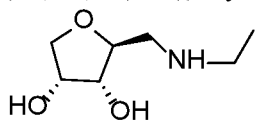
22. (2S,3R,4R)-2-(azidomethyl)tetrahydrofuran-3,4-diol



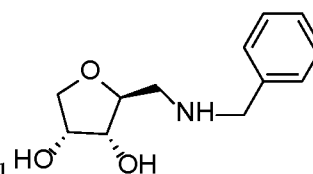
23. (2S,3R,4R)-2-(aminomethyl)tetrahydrofuran-3,4-diol



24. (2S,3R,4R)-2-((ethylamino)methyl)tetrahydrofuran-3,4-diol

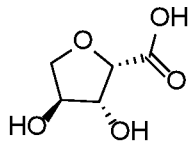


25. (2S,3R,4R)-2-((benzylamino)methyl)tetrahydrofuran-3,4-diol

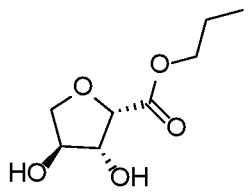


C) from anhydroxylitol:

1. (2S,3R,4S)-3,4-dihydroxytetrahydrofuran-2-carboxylic acid

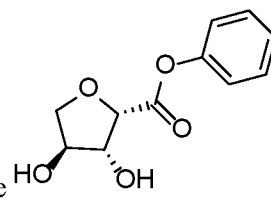


2. Propyl (2S,3R,4S)-3,4-dihydroxytetrahydrofuran-2-carboxylate

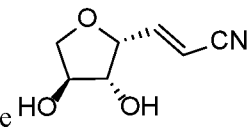


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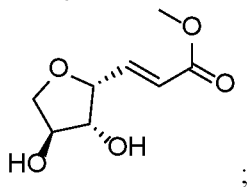
3. Phenyl (2S,3R,4S)-3,4-dihydroxytetrahydrofuran-2-carboxylate



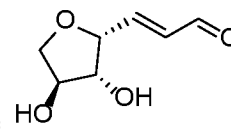
4. (E)-3-((2R,3R,4S)-3,4-dihydroxytetrahydrofuran-2-yl)acrylonitrile



5. Methyl (E)-3-((2R,3R,4S)-3,4-dihydroxytetrahydrofuran-2-yl)acrylate

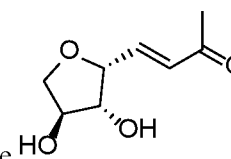


6. (E)-3-((2R,3R,4S)-3,4-dihydroxytetrahydrofuran-2-yl)acrylaldehyde

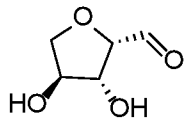


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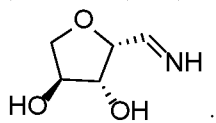
7. (E)-4-((2R,3R,4S)-3,4-dihydroxytetrahydrofuran-2-yl)but-3-en-2-one



8. (2S,3R,4S)-3,4-dihydroxytetrahydrofuran-2-carbaldehyde

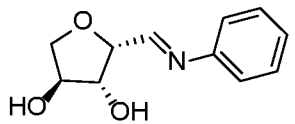


9. (2R,3R,4S)-2-(iminomethyl)tetrahydrofuran-3,4-diol

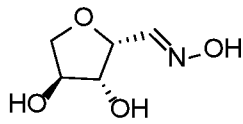


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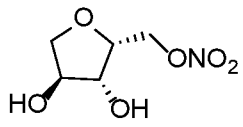
10. (2R,3R,4S)-2-((E)-(phenylimino)methyl)tetrahydrofuran-3,4-diol



11. (E)-3,4-dihydroxytetrahydrofuran-2-carbaldehyde oxime

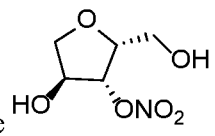


12. ((2R,3R,4S)-3,4-dihydroxytetrahydrofuran-2-yl)methyl nitrate

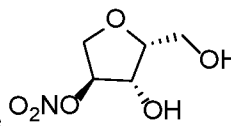


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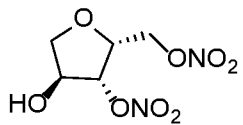
13. (2R,3R,4S)-4-hydroxy-2-(hydroxymethyl)tetrahydrofuran-3-yl nitrate



14. (3S,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl nitrate

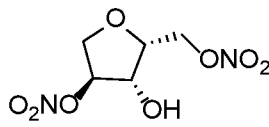


15. (2R,3R,4S)-4-hydroxy-2-((nitrooxy)methyl)tetrahydrofuran-3-yl nitrate

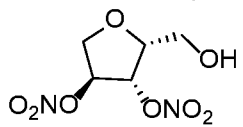


10

16. (3S,4S,5R)-4-hydroxy-5-((nitrooxy)methyl)tetrahydrofuran-3-yl nitrate

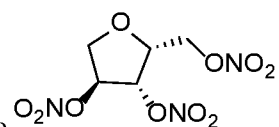


17. (2R,3S,4S)-2-(hydroxymethyl)tetrahydrofuran-3,4-diyl dinitrate

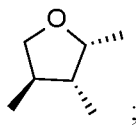


15

18. (2R,3S,4S)-2-((nitrooxy)methyl)tetrahydrofuran-3,4-diyl dinitrate



19. (2R,3R,4R)-2,3,4-trimethyltetrahydrofuran



20. (2R,3R,4S)-2-(((trimethylsilyl)oxy)methyl)tetrahydrofuran-3,4-diol

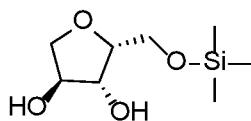


FIG. 1A.

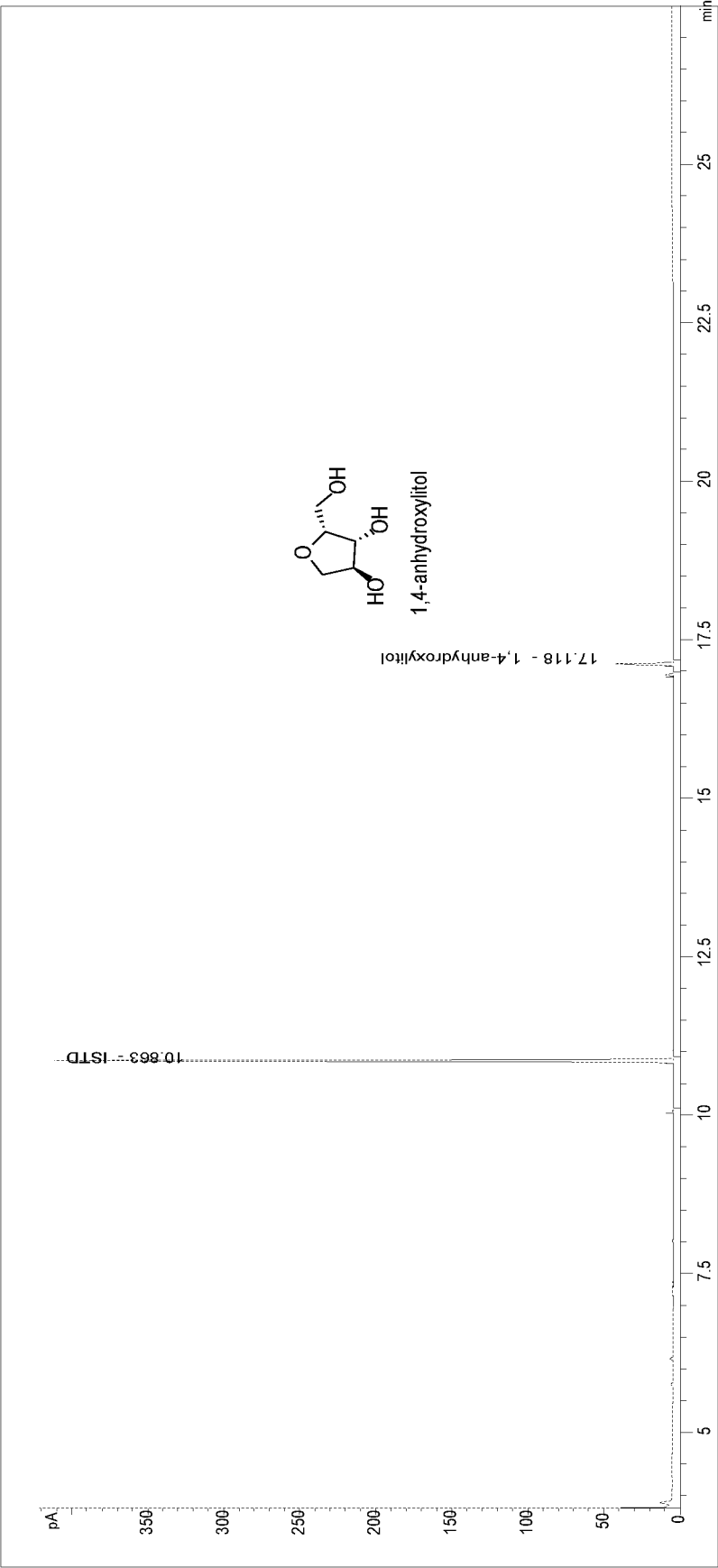


FIG. 1B.

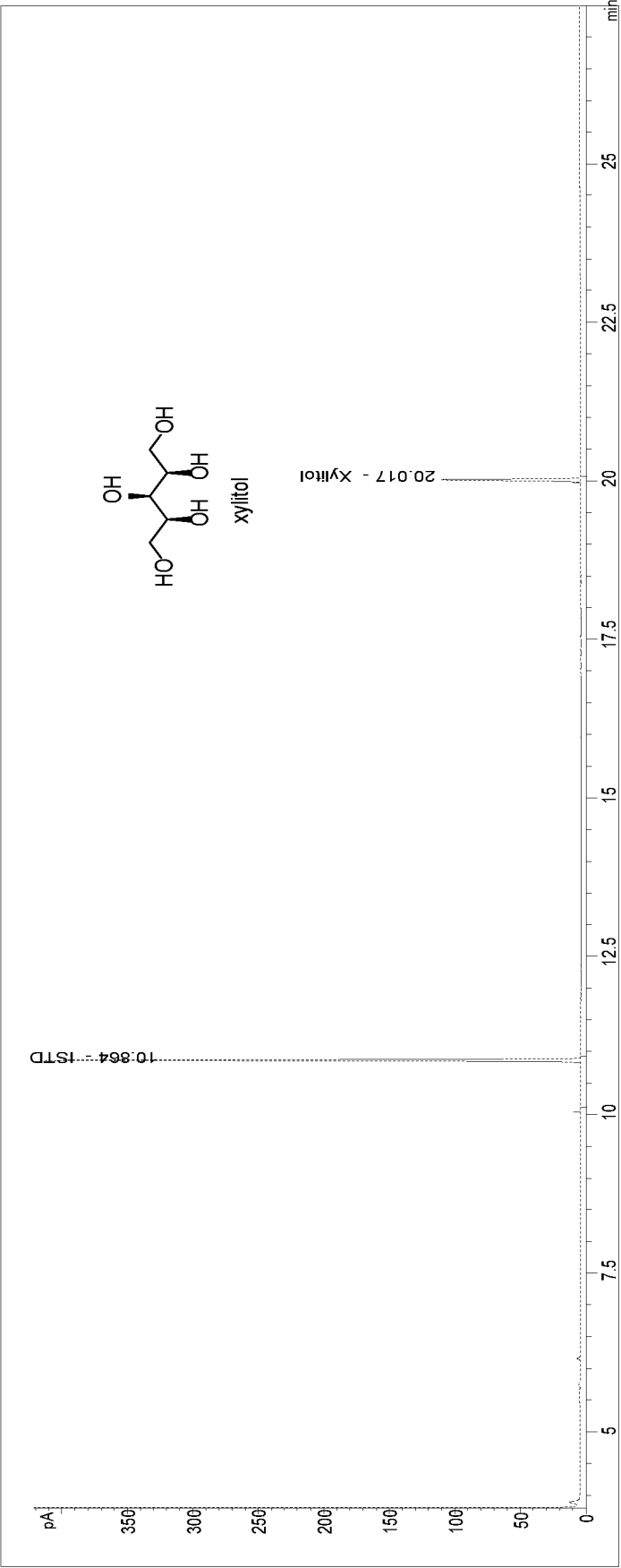


FIG. 2A.

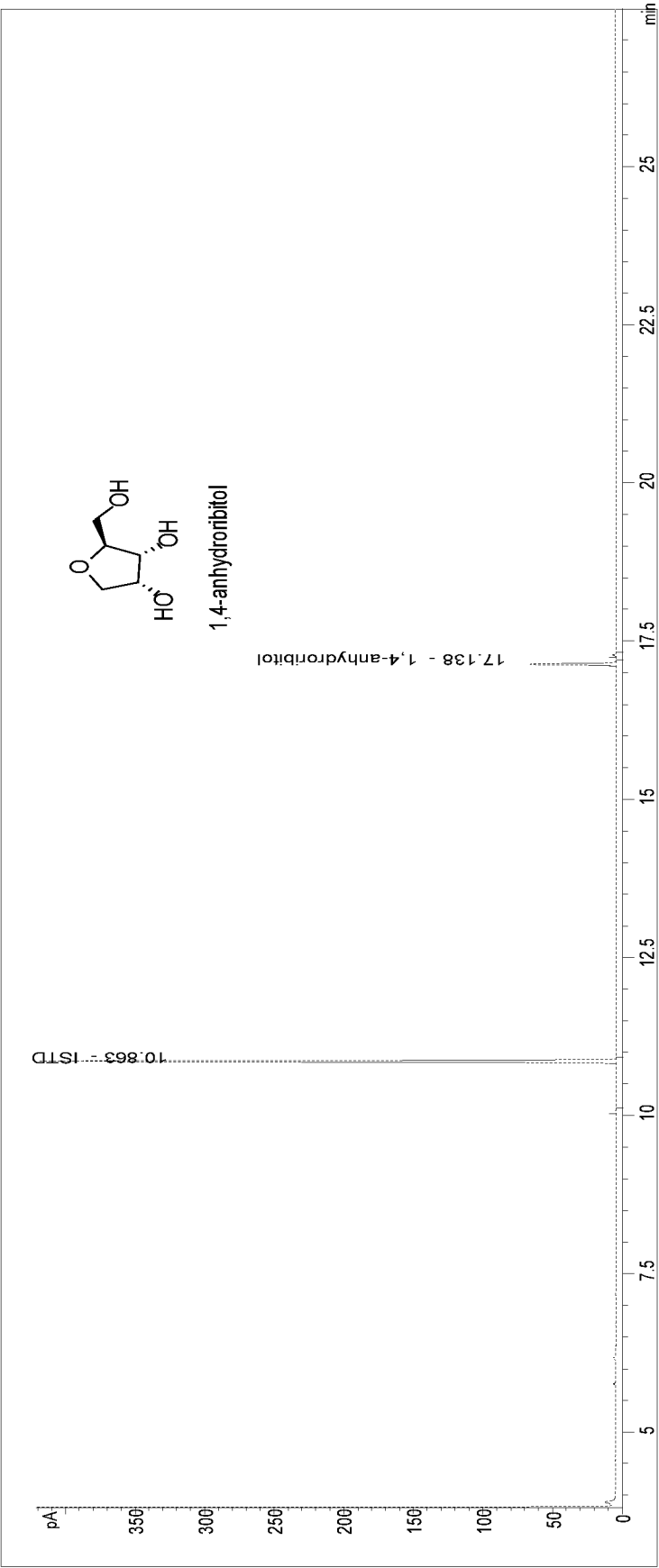


FIG. 2B.

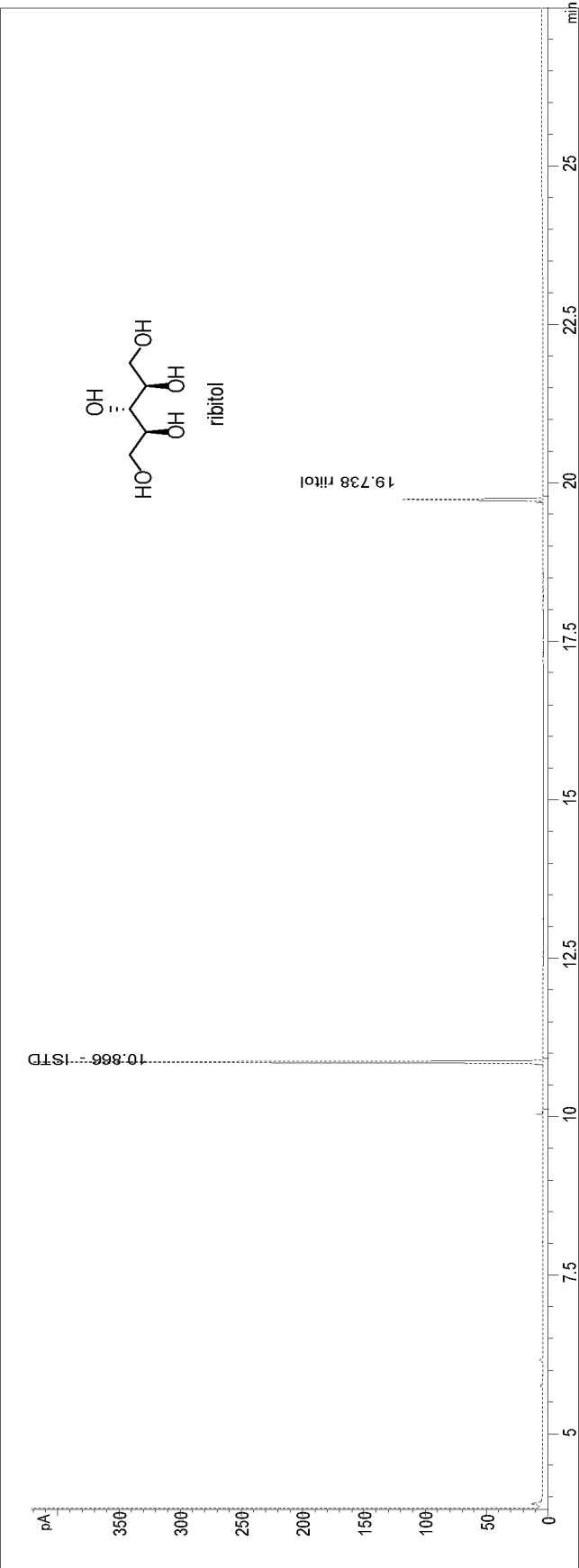


FIG. 3A.

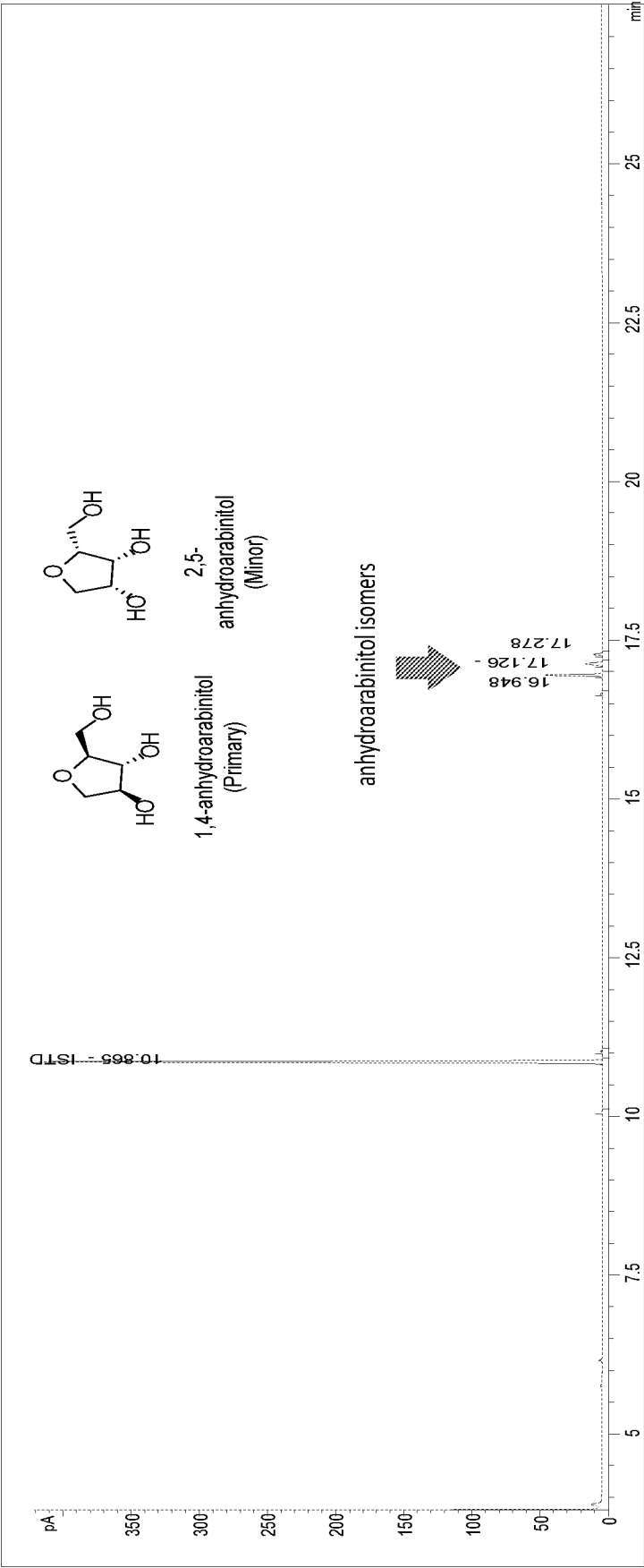
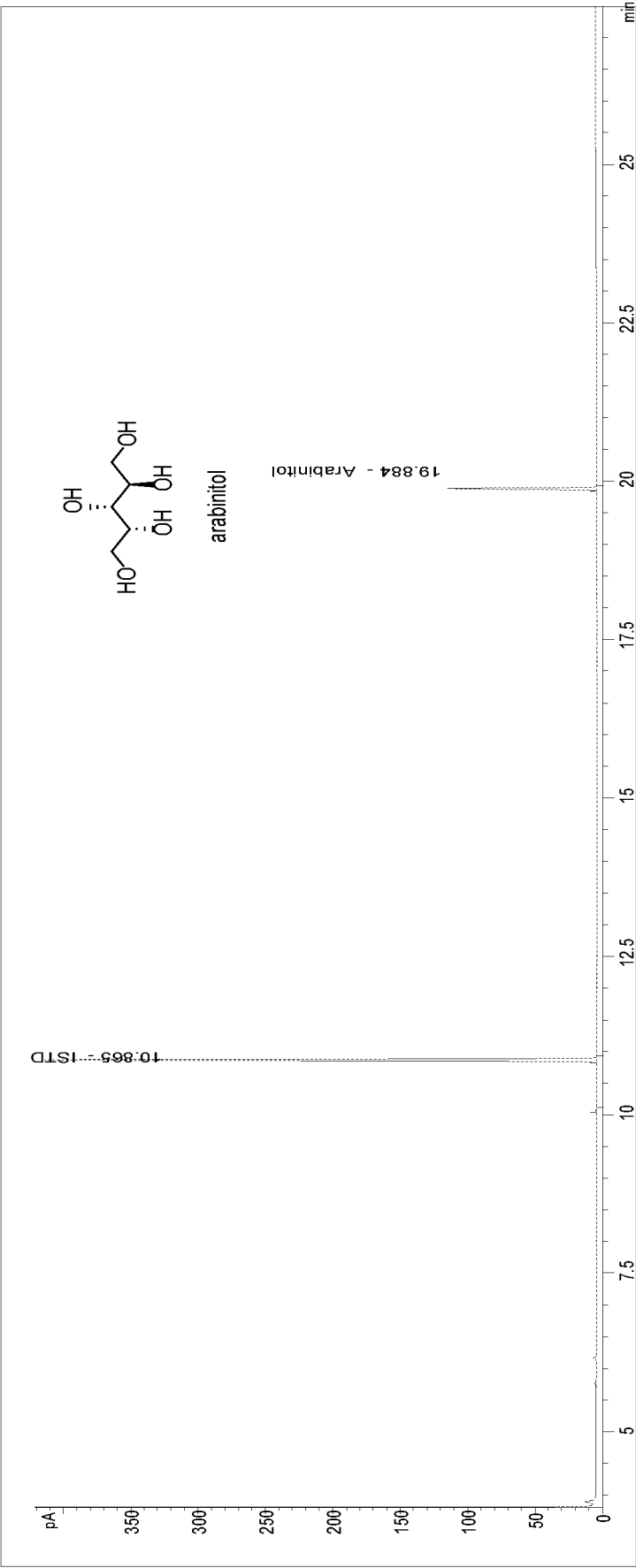


FIG. 3B.



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2016/041985**A. CLASSIFICATION OF SUBJECT MATTER****C07D 307/20(2006.01)i, B01J 31/12(2006.01)i**

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)

C07D 307/20; C07D 307/02; G01N 33/98; C07C 31/18; C13K 13/00; G01N 33/50; C12G 3/08; B01J 31/12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean utility models and applications for utility models

Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

eKOMPASS(KIPO internal), STN Express(Registry, Caplus, CASReact), Google &

Keywords: anhydropentitol, pentitol, water-tolerant Lewis acid, catalyst, dehydrate, cyclizate

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2014-137619 A1 (ARCHER DANIELS MIDLAND COMPANY) 12 September 2014	1-18
A	See abstract; paragraphs [0001], [0011], [0012]; and claims 1-7.	19, 20
Y	US 2004-0152907 A1 (MOORE, K. M. et al.) 5 August 2004	1-18
A	See abstract; paragraphs [0045]-[0047]; and claims 1, 27, 30.	19, 20
X	Chemical Abstract compound, STN express.	19, 20
A	See RN 728860-04-6 (Entered STN: 19 August 2004).	1-18
X	NORRILD, J. C. et al., "A new efficient and stereospecific conversion of aminodeoxyalditols into aminoalkyl-substituted tetrahydrofurans", Carbohydrate Research, 1996, Vol. 291, pages 85-98	19, 20
A	See abstract.	1-18
A	US 2013-0337570 A1 (HOWARD, S. et al.) 19 December 2013	1-20
	See abstract; paragraphs [0009], [0024]; and claim 12.	



Further documents are listed in the continuation of Box C.



See patent family annex.

* 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

29 November 2016 (29.11.2016)

Date of mailing of the international search report

29 November 2016 (29.11.2016)

Name and mailing address of the ISA/KR

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

PCT/US2016/041985

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014-137619 A1	12/09/2014	CN 105026542 A EP 2964743 A1 EP 2964743 A4 JP 2016-516014 A KR 10-2015-0123923 A US 2016-0016970 A1	04/11/2015 13/01/2016 13/07/2016 02/06/2016 04/11/2015 21/01/2016
US 2004-0152907 A1	05/08/2004	AU 2004-288802 A1 CA 2545914 A1 EP 1689697 A1 EP 1689697 A4 EP 1689697 B1 ES 2566667 T3 US 2002-0052516 A1 US 6849748 B2 US 7439352 B2 WO 2005-047228 A1	26/05/2005 26/05/2005 16/08/2006 31/10/2007 20/01/2016 14/04/2016 02/05/2002 01/02/2005 21/10/2008 26/05/2005
US 2013-0337570 A1	19/12/2013	EP 2684041 A2 EP 2684041 A4 JP 2014-511495 A KR 10-2014-0025379 A WO 2012-121913 A2 WO 2012-121913 A3	15/01/2014 10/09/2014 15/05/2014 04/03/2014 13/09/2012 31/01/2013