(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 June 2017 (15.06.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/100402 A1

(51) International Patent Classification:
C07D 307/20 (2006.01) *A61K 31/25* (2006.01)

(21) International Application Number:
PCT/US2016/065523

(22) International Filing Date:
8 December 2016 (08.12.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/266,043 11 December 2015 (11.12.2015) US

(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).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

Published:

— *with international search report (Art. 21(3))*

WO 2017/100402 A1

(54) Title: ONE-POT SYNTHESIS OF ANHYDROPENTITOL ESTERS FROM PENTITOLS, CATALYZED BY WATER-TOLERANT LEWIS ACIDS

(57) Abstract: A procedure for preparing anhydropentitol mono, di, and tri esters is described. The process is performed in a single vessel and involves sequential dehydrative cyclization and carboxylic acid acylation steps. Each step is catalyzed by low loadings of a water-tolerant Lewis acid catalyst. The method of synthesis is efficacious and depending on the reaction condition, generates modest to high yields of the target mono-, di-, and triesters. The esters can be practical surrogates of incumbent petroleum materials of similar structure used for surfactants and plasticizers.

ONE-POT SYNTHESIS OF ANHYDROPENTITOL ESTERS FROM PENTITOLS, CATALYZED BY WATER-TOLERANT LEWIS ACIDS

PRIORITY CLAIM

[0000] This Application claims benefit of priority of U.S. Provisional Application Nos. 62/205,340, filed August 14, 2015, and 62/266,043, filed December 11, 2015, the contents of each are incorporated herein by reference.

FIELD OF INVENTION

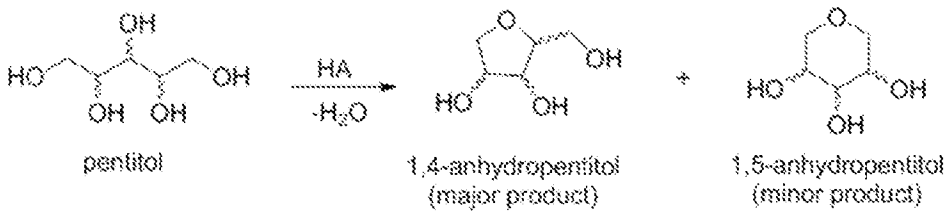
[0001] The present application relates to the preparation of esters from biologically derived molecules. In particular, the present disclosure describes preparation of mono, di, and triesters of anhydropentitols from sugar-derived triols.

BACKGROUND

[0002] Petroleum has been the predominant inexpensive source of hydrocarbons for the production of both commodity and specialty chemicals for over a century. In recent years as scientists have tried to find alternatives to petroleum-based hydrocarbons and develop more environmentally sustainable replacements from renewable carbon resources, they have often looked to carbon sources that can be derived from biomass. A major component of biomass is carbohydrates or sugars (i.e., hexoses and pentoses) that can be readily transformed into other versatile precursor molecules from which various other useful compounds can be prepared.

[0003] One class of precursors derived from pentoses that can be prepared readily by means of acid-catalyzed dehydrative cyclization of C_5 sugar alcohols (i.e., pentitols) are 1,4-anhydropentitols and 1,5-anhydropentitols. (See e.g., Chari, Ravi V. J. and Blattler, Walter A., Int'l. Appl. No. 2001/049698, 12 Jul 2001, Brønsted acid catalyzed dehydration of pentitols to anhydropentitols.) The dehydration reaction is shown in Scheme A.

Scheme A.



[0004] Anhydropentitols have considerable value as renewable molecular entities because of their intrinsic chiral tri-functionalities. Anhydropentitol molecules can serve as versatile precursors for certain derivatives that include tetrahydrofuranic structural analogs. This characteristic enables chemists to expand the potential to synthesize both existing and new derivative compounds. For

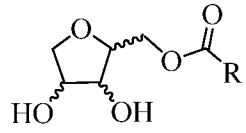
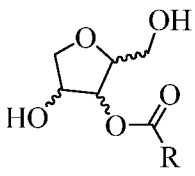
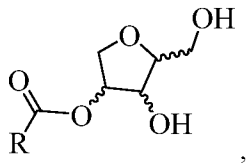
example, these compounds can serve as alternative precursors for naphthenes and other aliphatic cyclic molecules which traditionally have relied entirely on petrochemical processes for production. A particular attribute of anhydropentitols is that they encompass functionalities that are absent from fossil-based hydrocarbon materials, and such functional groups would otherwise need to be inserted chemically in complex multi-step syntheses to functionalize when starting from fossil-based hydrocarbons. Moreover, as cyclic furano-triols, the anhydropentitol molecules possess a structural similarity to other cyclic ester polyols. Anhydropentitols with such qualities can serve as surrogates for organic compounds that have been made traditionally from non-renewable petrochemical sources.

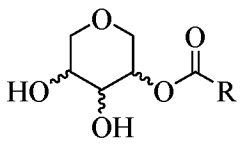
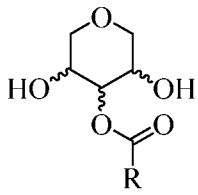
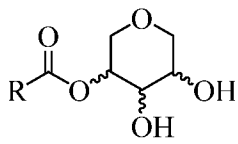
[0005] To better leverage the functional potential of anhydropentitols, a need exists for a simple and cost effective method of preparing derivative compounds from these molecule. For example, monoesters, diesters and triesters of anhydropentitols can serve as a ready platform for a variety of chemical transformations. Derivatives of anhydropentitol esters can be used to generate various chemical compounds from a renewable source material. These compounds may include, for instance, polymer subunits, plasticizers, lubricants, dispersants, emulsifiers, adhesives coatings, resins, or humectants and surfactants. Hence, a method that can make esters from the anhydropentitol molecules can promote further innovation in the synthesis and development of novel compounds to more efficiently capture the industrial potential of these molecules.

SUMMARY OF INVENTION

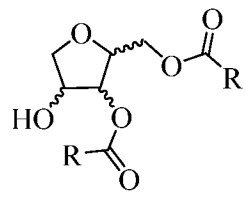
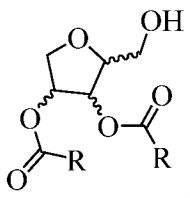
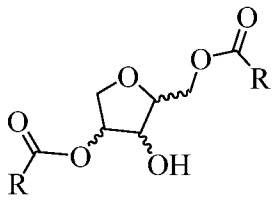
[0006] The present disclosure describes a method for converting monosaccharides into cyclized esters directly from a sugar alcohol. In particular, the process involves reacting a pentitol with an organic acid in the presence of a water-tolerant Lewis acid to form a cyclical anhydropentitol, and acylating the cyclical anhydropentitol with a carboxylic acid all within a single reaction vessel (i.e., "one-pot"). Hence, one can avoid the need for workup steps in between each transformation.

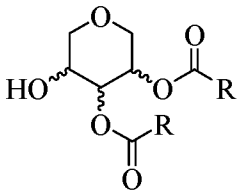
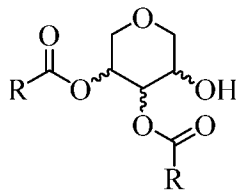
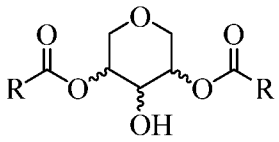
[0007] In another aspect, the present invention also relates to the mono-, di- or triester derivatives of the anhydropentitols. The anhydropentitol monoester has a structure according to at least one of the following:

a) , b) , c) ,

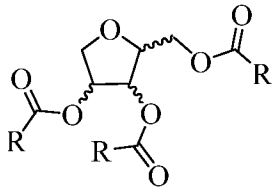
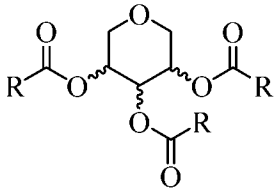
d) , e) , and f) , where R is an alkyl, alkenyl, alkynyl, allyl, or aromatic group.

[0008] The anhydropentitol diester has a structure according to at least one of the following:

a)  , b)  , c)  ,

d)  , e)  , and f)  , where R is an alkyl, alkenyl, alkynyl, allyl, or aromatic group.

[0009] The anhydropentitol triester has a structure according to at least one of the following:

a)  and b)  , where R is an alkyl, alkenyl, alkynyl, allyl, or aromatic group.

[0010] Additional features and advantages of the present synthesis process and material compounds 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.

BRIEF DESCRIPTION OF FIGURES

[0011] FIG. 1 is a schematic of a generic reaction illustrative of the present method in which pentitol-derived triol esters are prepared in a single-vessel by a) catalytically dehydrating the pentitol with a metal triflate ($M(OTf)_x$) catalyst and b) acylating the anhydropentitol product with a carboxylic acid using the same metal triflate catalyst.

[0012] FIG. 2 is a schematic of a reaction according to an embodiment of the present invention using xylitol and hexanoic acid to synthesize anhydroxylitol hexanoate mono-, di- and triesters using a metal triflate ($M(OTf)_x$) catalyst.

[0013] FIG. 3 is a gas chromatograph (GC) trace of the resulting product mixture from dehydrative cyclization and acylation of xylitol using 0.1 mol.% $Sc(OTf)_3$ catalyst to generate anhydroxylitol mono-, di- and trihexanoate species according to an embodiment of the present synthesis process.

[0014] FIG. 4 is a GC trace of products from dehydrative cyclization and acylation of arabitol using 0.1 mol.% $Hf(OTf)_4$ catalyst to produce anhydroarabitol mono-, di- and trihexanoates according to another embodiment.

[0015] FIG. 5 is a GC trace of products from dehydrative cyclization and acylation of ribitol using 0.1 mol.% $Ga(OTf)_3$ catalyst to yield anhydroribitol mono-, di- and trihexanoates according to another embodiment.

DETAILED DESCRIPTION OF INVENTION

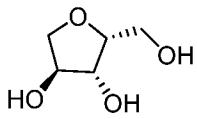
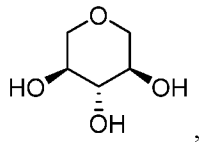
Section I. – Description

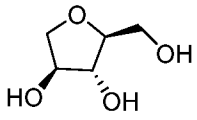
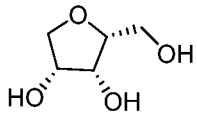
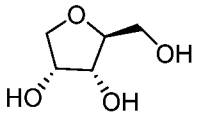
A.

[0016] The present disclosure describes, in part, a highly efficient process for preparation of anhydropentitol esters from pentitols. The conversion of a sugar alcohol to its anhydropentitol cyclic derivative and subsequent acylation can be performed all in a single reaction vessel (i.e., "one pot"). One-pot synthesis is a strategy to improve the efficiency of a chemical reaction whereby a reactant is subjected to successive chemical reactions in just one reactor. The strategy avoids a lengthy separation process and purification of the intermediate chemical compounds, and saves time and resources while increasing chemical yield.

[0017] Pentitols are a class of sugar alcohols that has good potential to serve as starting materials for derivative chemical platforms. In particular, pentitols include the reduction products of xylose, ribose, and arabinose. Anhydropentitol compounds, the dehydrated products of pentitols, can have a structure according to at least one of the following:

Scheme 1.

a) 1,4-anhydroxylitol , b) 1,5-anhydroxylitol ,

c) 1,4-anhydroarabinitol , d) 2,5-.anhydroarabinitol , and e) 1,4-anhydroribitol .

[0018] Anhydroxpentitols embody a versatile class of substrates that have not been well explored due to their relative commercial scarcity. As reagents, anhydropentitol molecules are appealing because they have three chiral functional centers, features *sui generis* for tetrahydrofuran substances, which further enables manifold, target-orientated synthetic approaches to be facilely adopted in the realization of novel materials with propitious chemical properties, such as polymer subunits, plasticizers, lubricants, dispersants, emulsifiers, adhesives coatings, resins, humectants and surfactants. It is envisioned that the mono-, di- and tri esters that can be synthesized by means of the

present method can be further modified and be transformed into other potential compounds, such as surfactants and plasticizers.

[0019] Generally, the present method involves performing a dehydrative cyclization with a linear pentitol in the presence of water-tolerant Lewis acid ("WTLA") catalysts, and subsequent acylation of the anhydropentitols with a carboxylic acid that is also catalyzed by the water-tolerant Lewis acid. 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. Traditionally, Lewis acids favor conditions in which virtually no water moisture is present, as they can quickly hydrolyze and lose their catalytic function even in with minor or trace amounts of water. As used herein, the term "water-tolerant" refers to a characteristic of a metal ion of a particular catalyst to resist being hydrolyzed by water to a high degree. 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). Descriptions of the properties of such materials are reviewed in *Chem Rev*, 2002, 3641-3666, the contents of which are incorporated herein by reference.

[0020] Water-tolerant Lewis acids, for example, may include one or more metal triflates selected from at least one of the following species: lanthanum triflate, cerium triflate, praseodymium triflate, neodymium triflate, samarium triflate, europium triflate, gadolinium triflate, terbium triflate, dysprodium triflate, holmium triflate, erbium triflate, ytterbium triflate, lutetium triflate, hafnium triflate, gallium triflate, scandium triflate, bismuth triflate, mercury triflate iron triflate, nickel triflate, copper triflate, zinc triflate, aluminum triflate, thallium, tin triflate, indium triflate, or a combination thereof. Certain effective triflate species include metals of hafnium, gallium, scandium, and bismuth.

[0021] The carboxylic acid can be a saturated or unsaturated aliphatic, aromatic or hetero-aromatic acid. Particular aliphatic carboxylic acid species can be selected from alkanoic, alkenoic, alkyonoic, and allylic acids having a carbon chain length ranging from C_2-C_{26}. Some examples of acids may include: hexanoic acid, stearic acid, acrylic acid, benzoic acid, phenyl acetic acid, or propiolic acid.

[0022] Figure 1 illustrates a general reaction to synthesize anhydropentitol mono, di, and triesters from pentitols according to the present method. The method involves using a water-tolerant Lewis acid catalyst to perform both a dehydrative cyclization of linear pentitols to cyclic anhydropentitols and subsequent acylation with a desired carboxylic acid. According to an embodiment, one can start with solid metal triflate and a solid sugar alcohol, such as arabitol, ribitol, or xylitol, with a liquid carboxylic acid. After melting the sugar alcohol and metal triflate and adding the carboxylic acid, the pentitol feed and carboxylic acid form a biphasic system, with the carboxylic acid in an upper phase layer and denser pentitol and WTLA catalyst in a more polar lower phase layer. The WTLA catalyst is immersed in the pentitol layer due to prevalent dipole-electrostatic attractions. Mediated by the WTLA catalyst, the pentitol then dehydrates in the denser lower phase to form anhydropentitol, which being more soluble in the carboxylic acid, diffuses along with the catalyst into the upper carboxylic acid layer, forming a single phase. The anhydropentitol then undergoes catalytic acylation in the

carboxylic acid layer. The anhydropentitol contacts the carboxylic acid at a reaction temperature and for a time sufficient to produce a mixture of corresponding ester derivatives of the anhydropentitol.

[0023] A particular example of the reaction is shown in Figure 2, which depicts formation of cyclic esters by reacting xylitol and hexanoic acid in the presence of the WTLA catalyst. According to the embodiment, the anhydroxylitol -OH moieties are either partially or fully acylated with said carboxylic acids, producing anhydroxylitol mono-, di-, and triesters. The reaction(s) can be conducted neat with a single carboxylic acid that serves as the acylating agent once the pentitol dehydration has occurred. Although one may use Brønsted acids to catalyze the dehydrative cyclization and acylation, water-tolerant Lewis acids, specifically metal triflates are surprisingly advantageous. Brønsted acids can be too harsh. For further detail about the dehydration reaction, see U.S. Provisional Application No. 62/205340 (Aug. 14, 2015), the contents of which are incorporated herein by reference.

[0024] The protocol for the catalytic dehydrative cyclization of pentitols to anhydropentitols is facile and high yielding. The process is able to converts the acyclic pentitols to a corresponding anhydropentitol at a yield of at least 50 mol.%, in typical embodiments the reaction can yield about 60 mol.% or 70 mol.% to about 85 mol.% or 90 mol.%, and in favored embodiments the conversion is near quantitative. The anhydropentitols can be converted to their corresponding cyclic esters in reasonably high yields of at least 50 mol.%. Typically in certain embodiments, the yield can be about 55 mol.% or 60 mol.% or 65-75% or 70-80 mol.%, depending on the reaction conditions. Optimized examples can reach yields of about 85-95% or greater to near complete conversion.

[0025] The esterification can be performed neat in the desired carboxylic acid at a certain temperature. The reaction is usually conducted in the temperature range of about 150°C to about 250°C, typically about 160°C to about 225°C, preferably about 170°C or 200°C, more preferably at about 170°C or 175°C to about 180°C, 190°C or 195°C. In a preferred process, use of a jacketed Dean-Stark trap is employed with a head space argon sweep, in which the water byproduct from condensation is immediately evaporated out of solution, hence driving the dehydration/acylation to completion.

[0026] The reaction time can be within 24 hours. Typically, the reaction time can be in a range from about 2 or 3 hours to about 15 or 20 hours; more typically from about 4 or 6 hours to about 10 or 12 hours (e.g., 5, 7, 8, 9, 11 hours).

[0027] In contrast to currently practiced commercial esterification protocols, which typically involve at more than 5 mol.% catalyst loadings relative to the amount of pentitol, the esterification method according to the present invention, may use catalysts in amounts of two or three orders of magnitude less to achieve congruent yields of esters, and hence are suitable in terms of moderating cost while concurrently augmenting the overall process efficiency. The present discovery that these catalysts can furnish relatively high diester yields (e.g., $\geq$ 55%-60%) at lower loads is highly desirable, and can reduce production costs.

[0028] The metal triflate catalyst can be present in an amount as little as about 0.001 mol.% relative to the amount of pentitol; ranging typically from about 0.01 mol.% to about 5 mol.% (e.g., 0.02 mol.%, 0.08 mol.%, 0.9 mol.%, 2 mol.%, or 3 mol.%). In certain examples, the amounts of catalyst loadings can range from about 0.03 mol.%, to about 1 mol.% (e.g., 0.05 mol.%, 0.07 mol.%, 0.1 mol.%, 0.3 mol.%, 0.5 mol.%, or 0.8 mol.%), manifesting a greater degree of anhydropentitol conversions and diester yields relative to conventional catalyst loading levels using Brønsted acids.

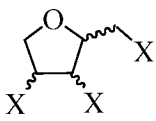
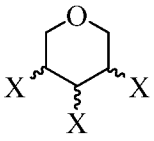
[0029] Another advantage of using water-tolerant Lewis acid catalysts (metal triflates) is that these catalysts can be recovered and reused, further saving reagent costs. A one-pot process that effects both the dehydrative cyclization and supervening acylation of pentitols with carboxylic acids deploying a single catalyst has been heretofore unknown.

B.

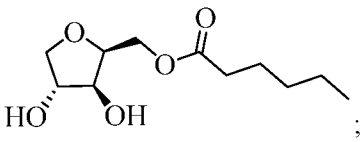
[0030] As will be further demonstrated in the examples of Section II, the metal triflates demonstrate a unique capability to catalyze effectively the conversion of pentitols to anhydropentitols and subsequent acylation of the anhydropentitols with carboxylic acids to produce corresponding anhydropentitol mono, di, and tri esters in copacetic yields.

[0031] As a starting material, the pentitol can be at least one of the following: D-arabinitol, D-ribitol, or D-xylitol. In the examples, an amount of pentitol is added to a three neck round bottomed flask equipped with a polytetrafluoroethylene (PTFE) coated magnetic stir bar. To the pentitol is added 0.1 mol.% (relative to the concentration of pentitol) of solid metal triflate catalyst, followed by a volume of hexanoic acid that corresponds to three molar equivalents. To the right-most neck is affixed a ground glass adapted argon inlet, the center neck a thermowell adapter, and the left-most neck a jacketed Dean-Stark (DS) trap filled with hexanoic acid and capped with a 14" needle-permeated rubber septum (argon outlet). While vigorously stirring, the pentitol suspension mixture is heated to a temperature about 175°C-190°C. At about 100°C, the pentitol melts and results in a clear phase separation. The high polarity of molten pentitol is believed to be an electrostatically preferable medium for the triflate salt. This is corroborated by the fact that no suspended solids are manifest in an upper carboxylic acid layer. At approximately 150°C, a profusion of water begins to assimilate in the glass tubing of the DS trap while the biphasic feature is maintained. As in the example of Figure 2, the sugar alcohol (xylitol) converts completely (quantitatively) to the anhydropentitol, and the biphasic quality of the mixture transforms into a single phase, indicative of the solubility of the anhydropentitol in hexanoic acid. The matrix darkened to a dull brown over the remaining two hours of the reaction, at which time aliquots were removed and analyzed by gas chromatography (GC). The results of GC analysis are presented in Figures 3, 4, and 5.

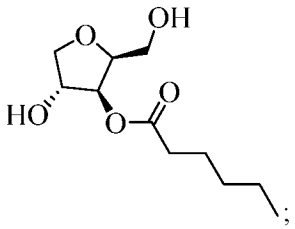
[0032] Expressed generally, the anhydropentitol ester compounds have a structure selected of:


and

, wherein X is a hydroxyl group or an ester moiety, and at least one X is the ester moiety. In particular examples when the ester moiety is a hexanoate moiety, according to certain embodiments using hexanoic acid, one can generate anhydropentitol monoesters having a structure such as one or more of the following:

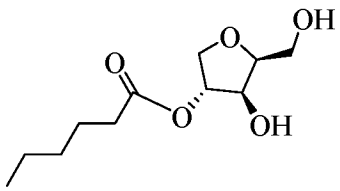
a. ((2S,3S,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl hexanoate


;

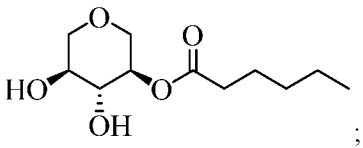
b. (2S,3S,4R)-4-hydroxy-2-(hydroxymethyl)tetrahydrofuran-3-yl hexanoate


;

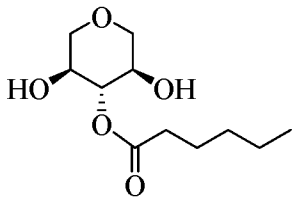
c. (3R,4R,5S)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl hexanoate


;

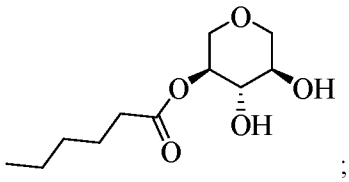
d. (3R,4R,5S)-4,5-dihydroxytetrahydro-2H-pyran-3-yl hexanoate


;

e. (3R,4R,5S)-3,5-dihydroxytetrahydro-2H-pyran-4-yl hexanoate

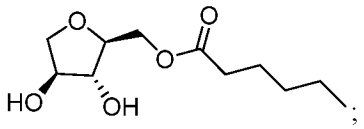

;

f. (3S,4S,5R)-4,5-dihydroxytetrahydro-2H-pyran-3-yl hexanoate



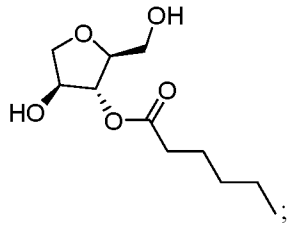
;

g. ((2S,3R,4S)-3,4-dihydroxytetrahydrofuran-2-yl)methyl hexanoate



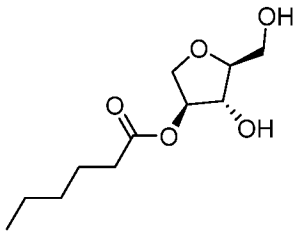
;

h. (2S,3R,4S)-4-hydroxy-2-(hydroxymethyl)tetrahydrofuran-3-yl hexanoate

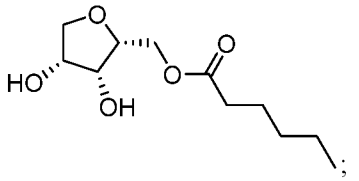


;

i. (3S,4S,5S)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl hexanoate

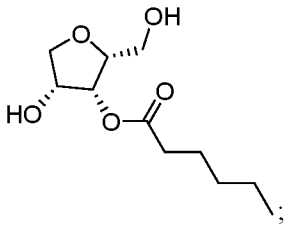


j. ((2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl hexanoate



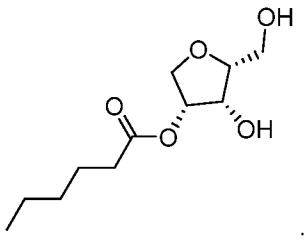
;

k. (2R,3R,4R)-4-hydroxy-2-(hydroxymethyl)tetrahydrofuran-3-yl hexanoate



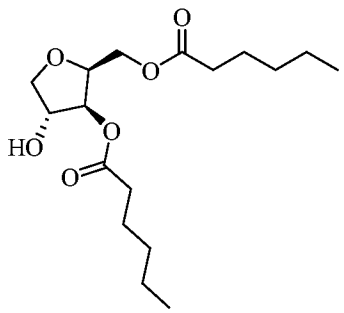
;

l. (3R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl hexanoate



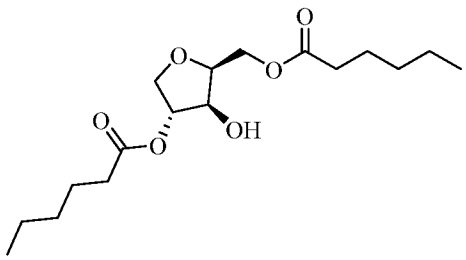
[0033] The anhydropentitol hexanoate diesters can have a structure such as one or more of the following:

a. ((2S,3S,4R)-3-(hexanoyloxy)-4-hydroxytetrahydrofuran-2-yl)methyl hexanoate

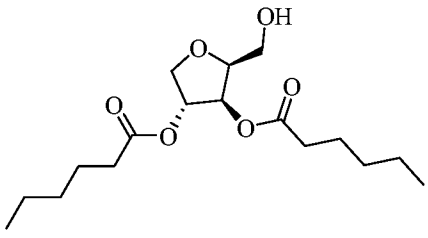


;

b. ((2S,3R,4R)-4-(hexanoyloxy)-3-hydroxytetrahydrofuran-2-yl)methyl hexanoate

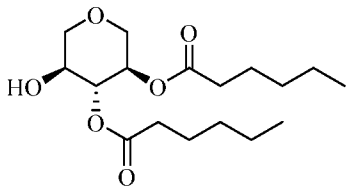


c. (2S,3R,4R)-2-(hydroxymethyl)tetrahydrofuran-3,4-diyl dihexanoate



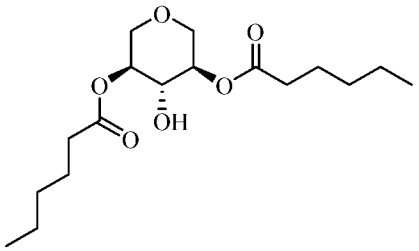
;

d. (3R,4R,5S)-5-hydroxytetrahydro-2H-pyran-3,4-diyl dihexanoate



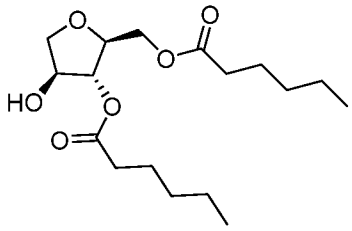
;

e. (3R,4R,5S)-4-hydroxytetrahydro-2H-pyran-3,5-diyl dihexanoate



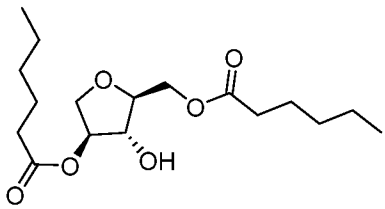
;

f. ((2S,3R,4S)-3-(hexanoyloxy)-4-hydroxytetrahydrofuran-2-yl)methyl hexanoate

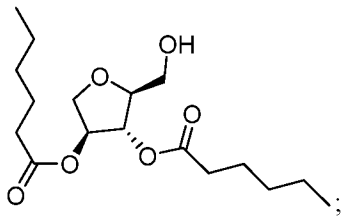


;

g. ((2S,3S,4S)-4-(hexanoyloxy)-3-hydroxytetrahydrofuran-2-yl)methyl hexanoate

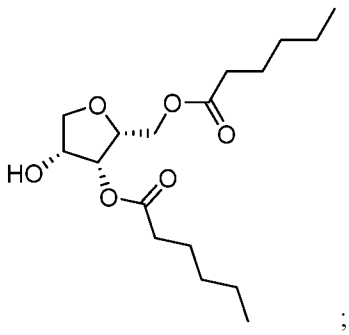


h. (2S,3S,4S)-2-(hydroxymethyl)tetrahydrofuran-3,4-diyl dihexanoate



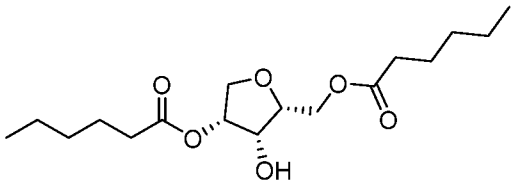
;

i. ((2R,3R,4R)-3-(hexanoyloxy)-4-hydroxytetrahydrofuran-2-yl)methyl hexanoate



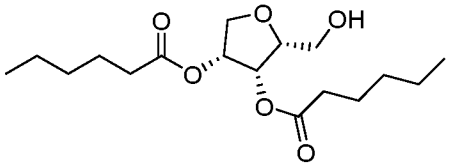
;

j. ((2R,3S,4R)-4-(hexanoyloxy)-3-hydroxytetrahydrofuran-2-yl)methyl hexanoate



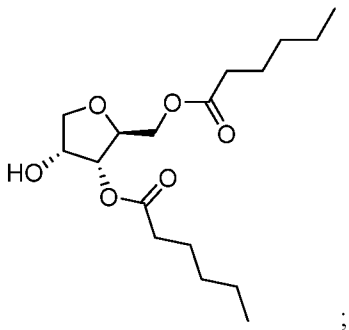
;

k. (2R,3S,4R)-2-(hydroxymethyl)tetrahydrofuran-3,4-diyl dihexanoate



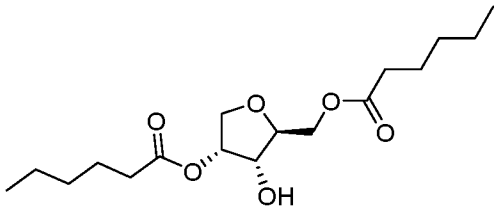
;

l. ((2S,3R,4R)-3-(hexanoyloxy)-4-hydroxytetrahydrofuran-2-yl)methyl hexanoate



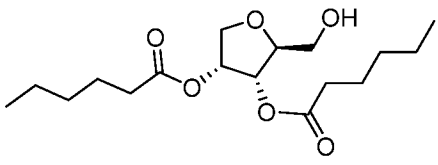
;

m. ((2S,3S,4R)-4-(hexanoyloxy)-3-hydroxytetrahydrofuran-2-yl)methyl hexanoate



;

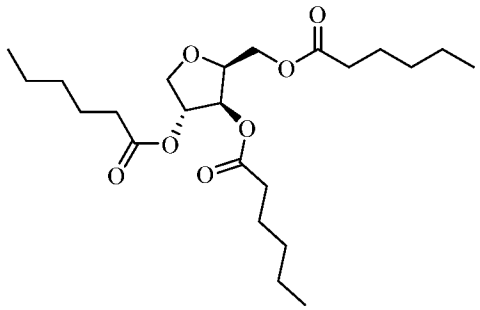
n. (2S,3S,4R)-2-(hydroxymethyl)tetrahydrofuran-3,4-diyl dihexanoate



.

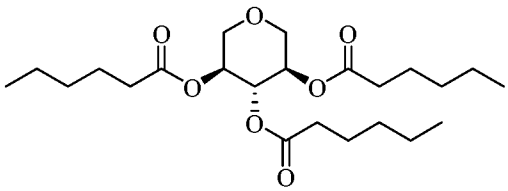
[0034] Further the anhydropentitol hexanoate triesters can have a structure such as one or more of the following:

a. (2S,3R,4R)-2-((hexanoyloxy)methyl)tetrahydrofuran-3,4-diyl dihexanoate



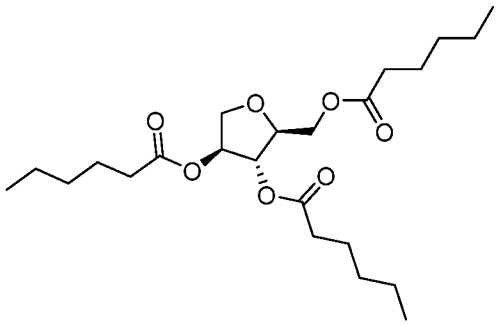
;

b. (3R,4r,5S)-tetrahydro-2H-pyran-3,4,5-triyl trihexanoate



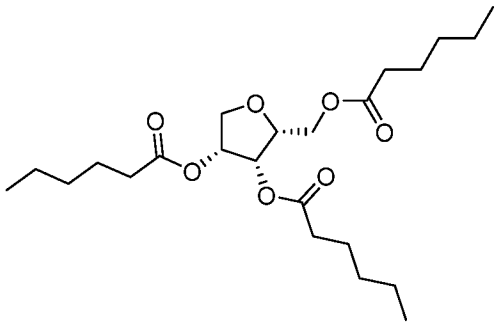
;

c. (2S,3S,4S)-2-((hexanoyloxy)methyl)tetrahydrofuran-3,4-diyl dihexanoate



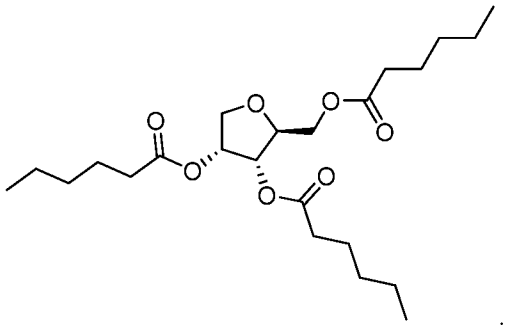
;

d. (2R,3S,4R)-2-((hexanoyloxy)methyl)tetrahydrofuran-3,4-diyl dihexanoate



;

e. (2S,3S,4R)-2-((hexanoyloxy)methyl)tetrahydrofuran-3,4-diyl dihexanoate



Section II. – Empirical Examples

[0035] The present method is further illustrated in the following examples. The examples use low catalytic amounts of water-tolerant homogeneous catalysts (in particular, scandium triflate, hafnium triflate, and gallium triflate) to dehydrate and cyclize xylitol, arabinitol, and ribitol (also known as adonitol) to their corresponding anhydropentitols. The starting C_5 sugar alcohols can be readily obtained commercially. Each example was executed in a facile "one-pot" system, using a single reaction vessel according to the present highly efficient method.

[0036] Example 1: Scandium triflate-mediated conversion of xylitol to anhydroxylitol mono, di and trihexanoates

Experimental: A three-necked, 500 mL round bottomed flask equipped with a PTFE-coated magnetic stir bar was charged with 100 g of xylitol (0.657 mol), 323 mg of $Sc(OTf)_3$ (0.1 mol%), and 250 mL of 1-hexanol (2.63 mol, 4 eq.) A jacketed Dean-Stark trap stoppered with a 12 gauge needle penetrated rubber septum was affixed to the leftmost neck, a thermowell adapter to the center, and an argon inlet to the rightmost neck. While vigorously stirring and under an argon sweep, the mixture was heated to 180°C for 8 h. After time, the mixture was cooled to ambient temperature and an aliquot withdrawn for GC analysis. Figure 3 presents the GC analysis result for the anhydroxylitol mono-, di- and triester species, which manifested three clusters of peaks: A) 19-21 minutes retention times pertaining to anhydroxylitol monohexanoates; B) 28-29 minutes retention times, pertaining to anhydroxylitol dihexanoates; 35-36 minutes retention times relating to anhydroxylitol trihexanoates.

[0037] Example 2: Hafnium triflate-mediated conversion of arabitol to anhydroarabitol mono, di and trihexanoates

Experimental: A three-necked, 500 mL round bottomed flask equipped with a PTFE-coated magnetic stir bar was charged with 100 g of arabitol (0.657 mol), 509 mg of $Hf(OTf)_4$ (0.1 mol%), and 250 mL of 1-hexanol (2.63 mol, 4 eq.) A jacketed Dean-Stark trap stoppered with a 12 gauge needle penetrated rubber septum was affixed to the leftmost neck, a thermowell adapter to the center, and an argon inlet to the rightmost neck. While vigorously stirring and under an argon sweep, the

mixture was heated to 180°C for 8 h. After time, the mixture was cooled to ambient temperature and an aliquot withdrawn for GC analysis. Figure 4 shows the GC analysis result of the anhydroarabitol mono-, di-, and triester species, which manifested two clusters of peaks: A) 19-21 minutes retention times pertaining to anhydroarabitol mono-hexanoates; and B) 28-29 minutes retention times, pertaining to anhydroarabitol di-hexanoates; C) 32-33 minutes retention times relating to anhydroarabitol trihexanoates.

[0038] Example 3: Gallium triflate-mediated conversion of ribitol to anhydroribitol mono, di and trihexanoates

Experimental: A three-necked, 500 mL round bottomed flask equipped with a PTFE-coated magnetic stir bar was charged with 100 g of ribitol (0.657 mol), 340 mg of $Ga(OTf)_3$ (0.1 mol%), and 250 mL of 1-hexanol (2.63 mol, 4 eq.) A jacketed Dean-Stark trap stoppered with a 12 gauge needle penetrated rubber septum was affixed to the leftmost neck, a thermowell adapter to the center, and an argon inlet to the rightmost neck. While vigorously stirring and under an argon sweep, the mixture was heated to 180°C for 8 h. After time, the mixture was cooled to ambient temperature and an aliquot withdrawn for GC analysis. Figure 5 shows the GC analysis of the resulting anhydroribitol mono-, di-, and triester species, which manifested two clusters of peaks: A) 19-21 minutes retention times pertaining to anhydroribitol monohexanoate; B) 28-29 minutes retention times pertaining to anhydroribitol dihexanoates; C) 35-36 minutes retention times relating to anhydroribitol trihexanoate.

[0039] 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:

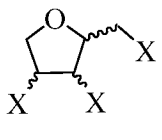
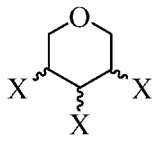
1. A method for preparing cyclic esters comprising: contacting a pentitol with an organic acid in the presence of a water-tolerant Lewis acid, at a reaction temperature and time sufficient to dehydrate said pentitol and form a cyclical anhydropentitol, and acylating said cyclical anhydropentitol with a carboxylic acid.
2. The method according to claim 1, wherein both dehydration and acylation reactions are performed within a single reaction vessel.
3. The method according to claim 1, wherein said pentitol is at least one of the following: D-ribitol, D-arabinitol, or D-xylitol.
4. The method according to claim 1, wherein said carboxylic acid is either a saturated or unsaturated aliphatic, aromatic or hetero-aromatic acid.
5. The method according to claim 4, wherein said carboxylic acid is selected from an alkanoic, alkenoic, alkyonoic acid having a carbon chain length ranging from C_2-C_{26}.
6. The method according to claim 1, wherein said cyclic anhydropentitol product from the dehydration of said pentitol is at least one of the following: 1,4-anhydroxylitol, 1,5-anhydroxylitol, 1,4-anhydroarabinitol, 2,5-anhydroarabinitol, and 1,4-anhydroribitol.
7. The method according to claim 1, wherein said water tolerant Lewis acid is a triflate of a metal selected from the group consisting of: lanthanum, cerium, praseodymium, neodymium, samarium, europium, gadolinium, terbium, dysprodium, holmium, erbium, ytterbium, lutetium, hafnium, gallium, scandium, bismuth, mercury, iron, nickel, copper, zinc, aluminum, thallium, tin, and indium.
8. The method according to claim 7, wherein said metal is at least one of: hafnium, gallium, scandium, and bismuth.
9. The method according to claim 1, wherein said water tolerant Lewis acid is present at a catalyst loading range from 0.001 mol.% to 5 mol.% relative to an amount of penitiol.
10. The method according to claim 9, wherein said catalyst loading is about 0.01 mol.% to about 0.1 mol.% relative to an amount of pentitol.
11. The method according to claim 1, wherein said reaction temperature ranges from about 150°C to about 250°C.
12. The method according to claim 11, wherein said reaction temperature is about 170°C to about 195°C.
13. The method according to claim 1, wherein said reaction time is within 24 hours.
14. The method according to claim 13, wherein said reaction time is in a range from about 2-12 hours.

15. The method according to claim 1, wherein said the metal triflate converts said pentitol to a corresponding anhydropentitol in a yield of at least 50 mol.%.

16. The method according to claim 15, wherein said yield of anhydropentitol is about 60 mol.% to about 95 mol.%.

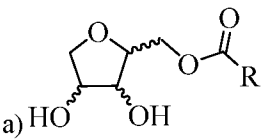
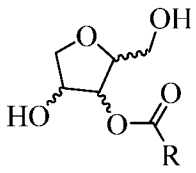
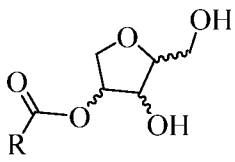
17. The method according to claim 1, wherein said the metal triflate converts said anhydropentitol to a corresponding mono-, di-, and triester in the presence of a carboxylic acid at a yield of at least 50 mol.%.

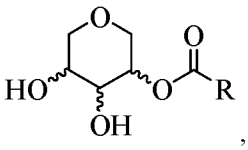
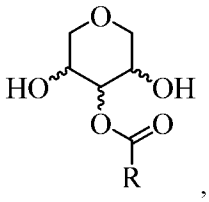
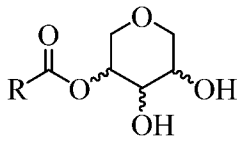
18. An anhydropentitol ester compound having a structure selected from the group consisting of:


and

,

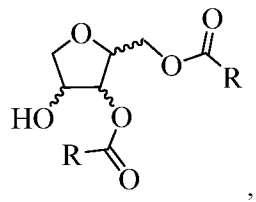
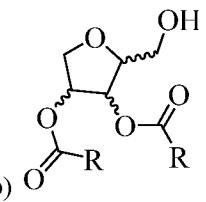
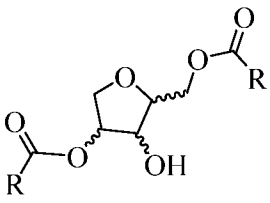
wherein X is a hydroxyl group or an ester moiety, and at least one X is the ester moiety.

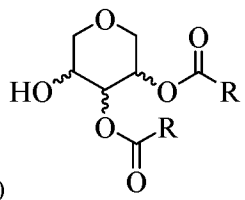
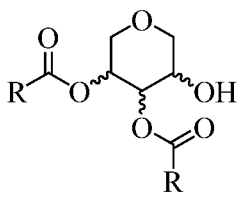
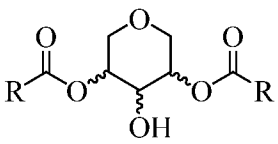
19. The anhydropentitol ester according to claim 18, wherein said anhydropentitol ester compound is a monoester having a structure according to at least one of the following:

a) 
, b) 
, c) 
, d)

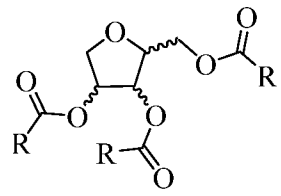

, e) 
, and f) 
, where R is an alkyl, alkenyl, alkynyl, allyl, or aromatic group.

20. The anhydropentitol ester according to claim 18, wherein said anhydropentitol ester compound is a diester having a structure according to at least one of the following:

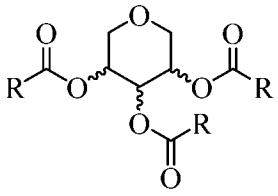
a) 
, b) 
, c) 
,

d) 
, e) 
, and f) 
, where R is an alkyl, alkenyl, alkynyl, allyl, or aromatic group.

21. The anhydropentitol ester according to claim 18, wherein said anhydropentitol ester compound is a triester having a structure according to at least one of the following:


a)

and b)

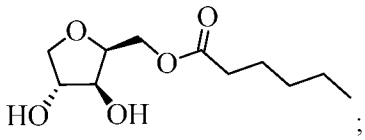


, where R is an alkyl, alkenyl, alkynyl, allyl, or aromatic group.

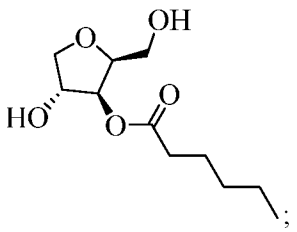
22. The anhydropentitol ester compound according to claim 18, wherein said ester moiety is a hexanoate moiety.

23. The anhydropentitol monoester according to claim 19, wherein said anhydropentitol monoester is one or more of the following:

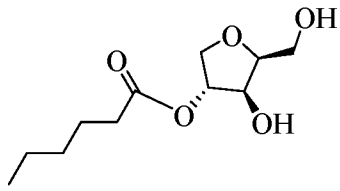
a. ((2S,3S,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl hexanoate


;

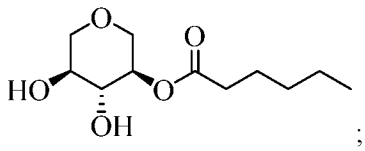
b. (2S,3S,4R)-4-hydroxy-2-(hydroxymethyl)tetrahydrofuran-3-yl hexanoate


;

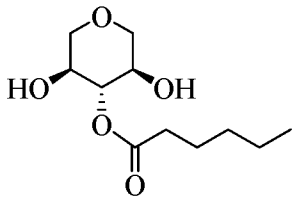
c. (3R,4R,5S)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl hexanoate


;

d. (3R,4R,5S)-4,5-dihydroxytetrahydro-2H-pyran-3-yl hexanoate

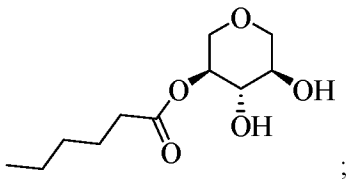

;

e. (3R,4R,5S)-3,5-dihydroxytetrahydro-2H-pyran-4-yl hexanoate



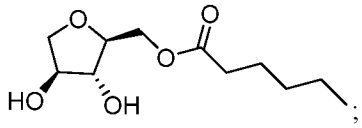
;

f. (3S,4S,5R)-4,5-dihydroxytetrahydro-2H-pyran-3-yl hexanoate



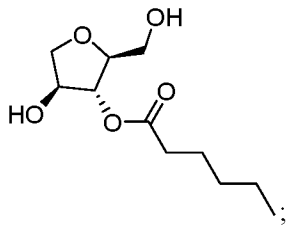
;

g. ((2S,3R,4S)-3,4-dihydroxytetrahydrofuran-2-yl)methyl hexanoate



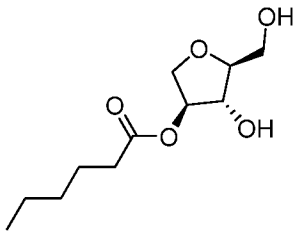
;

h. (2S,3R,4S)-4-hydroxy-2-(hydroxymethyl)tetrahydrofuran-3-yl hexanoate

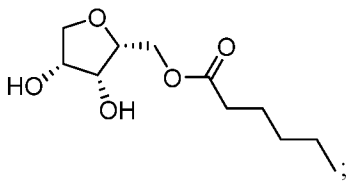


;

i. (3S,4S,5S)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl hexanoate

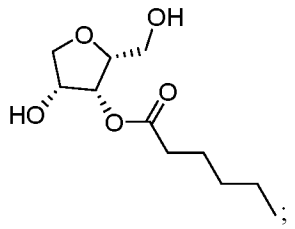


j. ((2R,3R,4R)-3,4-dihydroxytetrahydrofuran-2-yl)methyl hexanoate



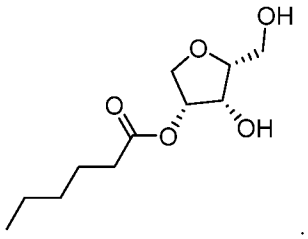
;

k. (2R,3R,4R)-4-hydroxy-2-(hydroxymethyl)tetrahydrofuran-3-yl hexanoate



;

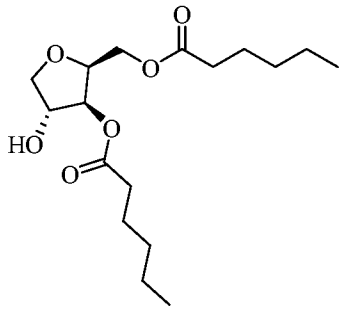
l. (3R,4S,5R)-4-hydroxy-5-(hydroxymethyl)tetrahydrofuran-3-yl hexanoate



.

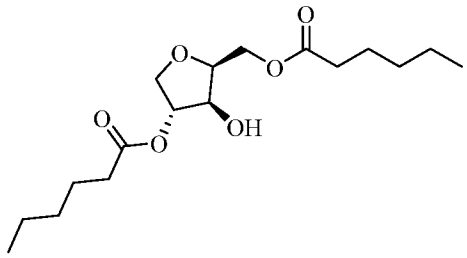
24. The anhydropentitol diester according to claim 20, wherein said anhydropentitol diester is one or more of the following:

a. ((2S,3S,4R)-3-(hexanoyloxy)-4-hydroxytetrahydrofuran-2-yl)methyl hexanoate

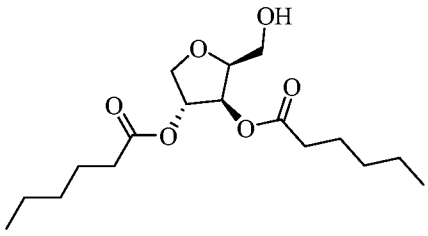


;

b. ((2S,3R,4R)-4-(hexanoyloxy)-3-hydroxytetrahydrofuran-2-yl)methyl hexanoate

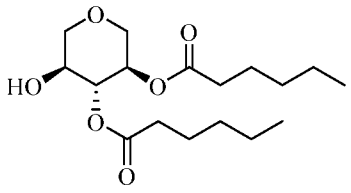


c. (2S,3R,4R)-2-(hydroxymethyl)tetrahydrofuran-3,4-diyl dihexanoate



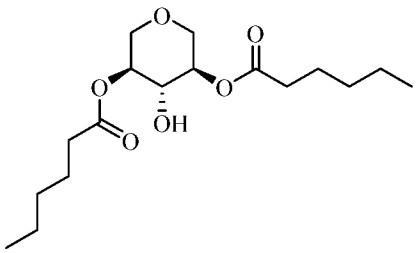
;

d. (3R,4R,5S)-5-hydroxytetrahydro-2H-pyran-3,4-diyl dihexanoate



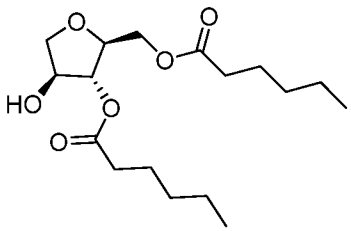
;

e. (3R,4R,5S)-4-hydroxytetrahydro-2H-pyran-3,5-diyl dihexanoate



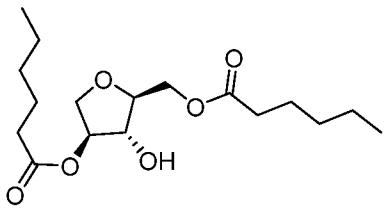
;

f. ((2S,3R,4S)-3-(hexanoyloxy)-4-hydroxytetrahydrofuran-2-yl)methyl hexanoate

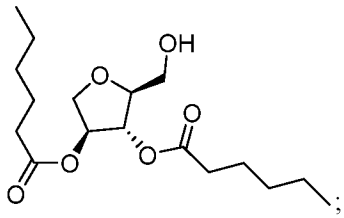


;

g. ((2S,3S,4S)-4-(hexanoyloxy)-3-hydroxytetrahydrofuran-2-yl)methyl hexanoate

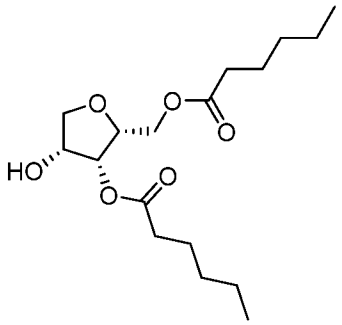


h. (2S,3S,4S)-2-(hydroxymethyl)tetrahydrofuran-3,4-diyl dihexanoate



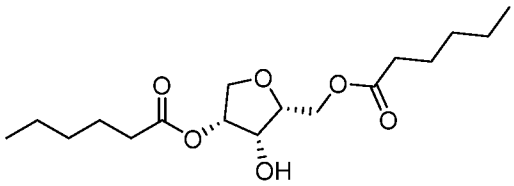
;

i. ((2R,3R,4R)-3-(hexanoyloxy)-4-hydroxytetrahydrofuran-2-yl)methyl hexanoate



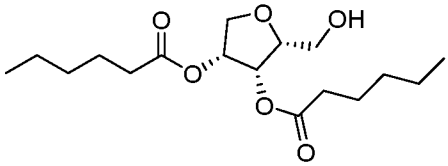
;

j. ((2R,3S,4R)-4-(hexanoyloxy)-3-hydroxytetrahydrofuran-2-yl)methyl hexanoate



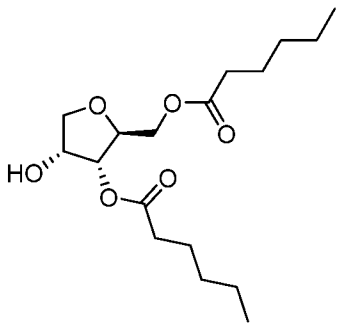
;

k. (2R,3S,4R)-2-(hydroxymethyl)tetrahydrofuran-3,4-diyl dihexanoate



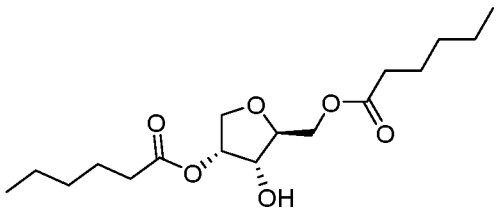
;

l. ((2S,3R,4R)-3-(hexanoyloxy)-4-hydroxytetrahydrofuran-2-yl)methyl hexanoate



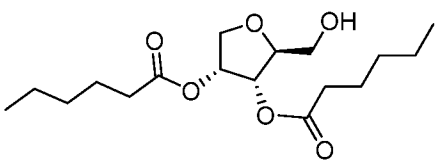
;

m. ((2S,3S,4R)-4-(hexanoyloxy)-3-hydroxytetrahydrofuran-2-yl)methyl hexanoate



;

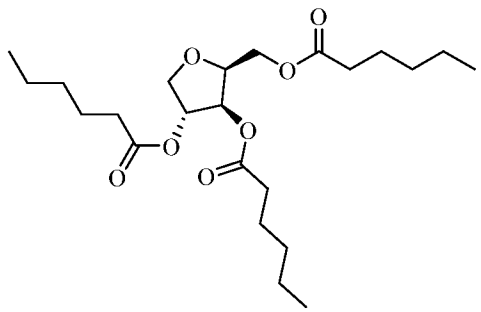
n. (2S,3S,4R)-2-(hydroxymethyl)tetrahydrofuran-3,4-diyl dihexanoate



.

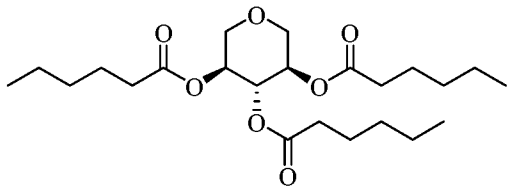
25. The anhydropentitol tri-ester according to claim 21, wherein said anhydropentitol triester is one or more of the following:

a. (2S,3R,4R)-2-((hexanoyloxy)methyl)tetrahydrofuran-3,4-diyl dihexanoate



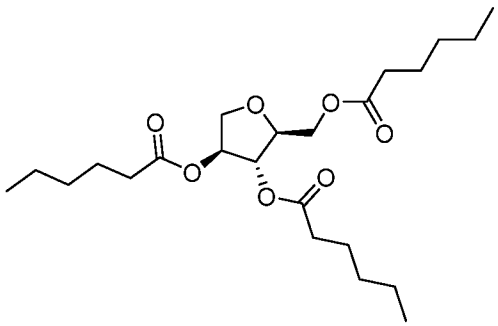
;

b. (3R,4r,5S)-tetrahydro-2H-pyran-3,4,5-triyl trihexanoate



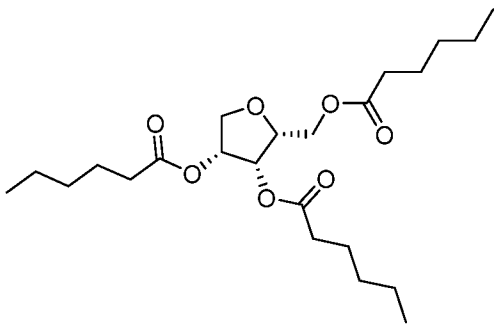
;

c. (2S,3S,4S)-2-((hexanoyloxy)methyl)tetrahydrofuran-3,4-diyl dihexanoate



;

d. (2R,3S,4R)-2-((hexanoyloxy)methyl)tetrahydrofuran-3,4-diyl dihexanoate



;

e. (2S,3S,4R)-2-((hexanoyloxy)methyl)tetrahydrofuran-3,4-diyl dihexanoate

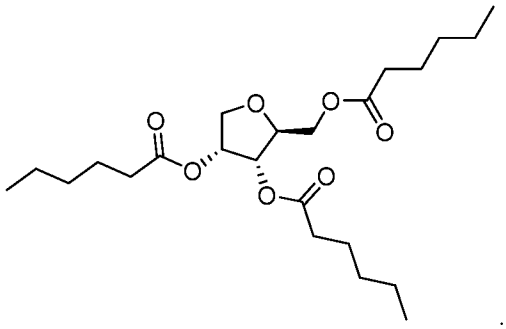


FIG. 1.

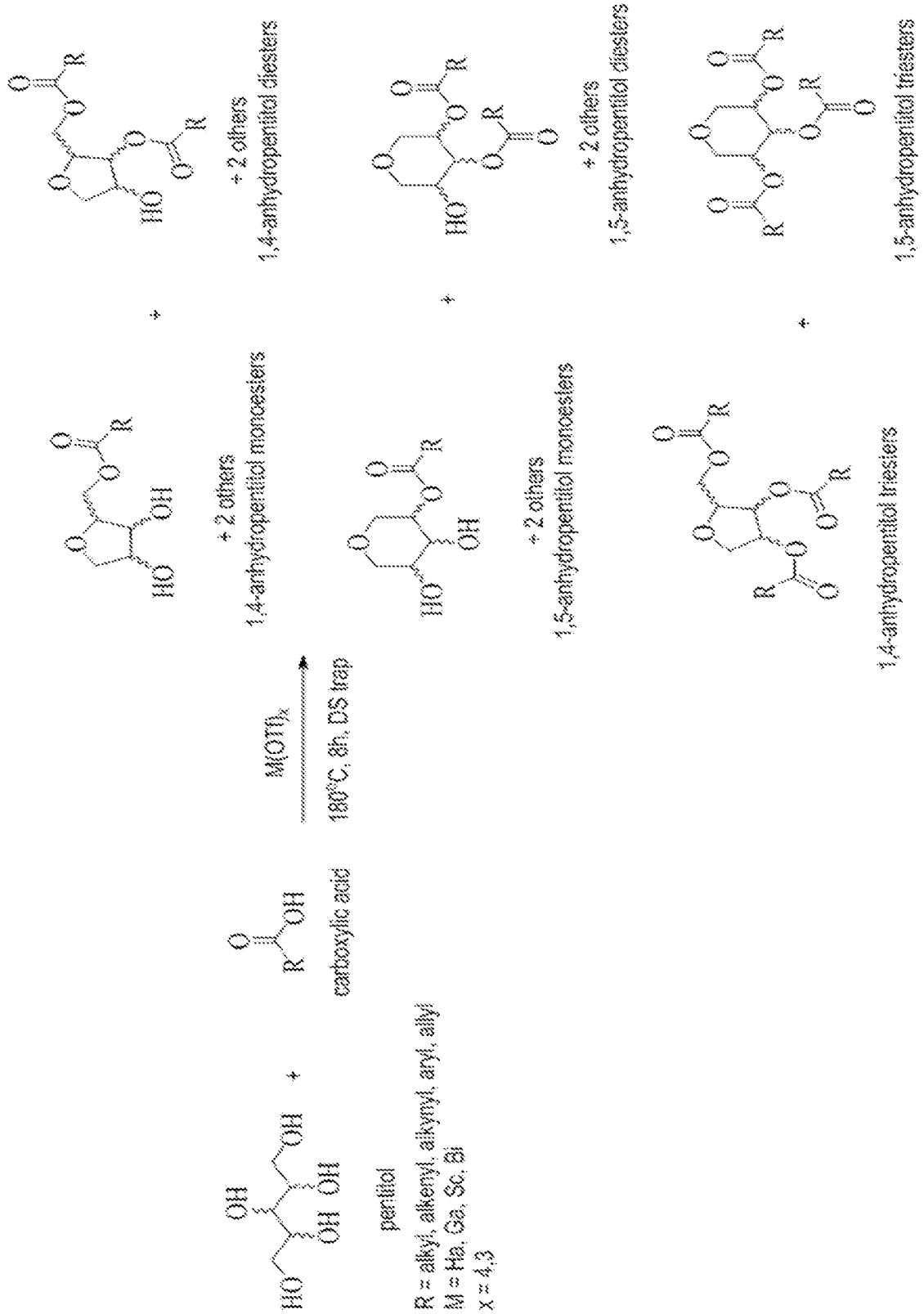

pentitol
R = alkyl, alkenyl, alkynyl, aryl, allyl
M = Ha, Ga, Sc, Bi
x = 4,3
carboxylic acid
M(OTf)x
180°C, 8h, DS trap
+ 2 others
1,4-anhydropentitol monoesters
+ 2 others
1,4-anhydropentitol diesters
+ 2 others
1,5-anhydropentitol monoesters
+ 2 others
1,5-anhydropentitol diesters
1,4-anhydropentitol triesters
1,5-anhydropentitol triesters

FIG. 2.

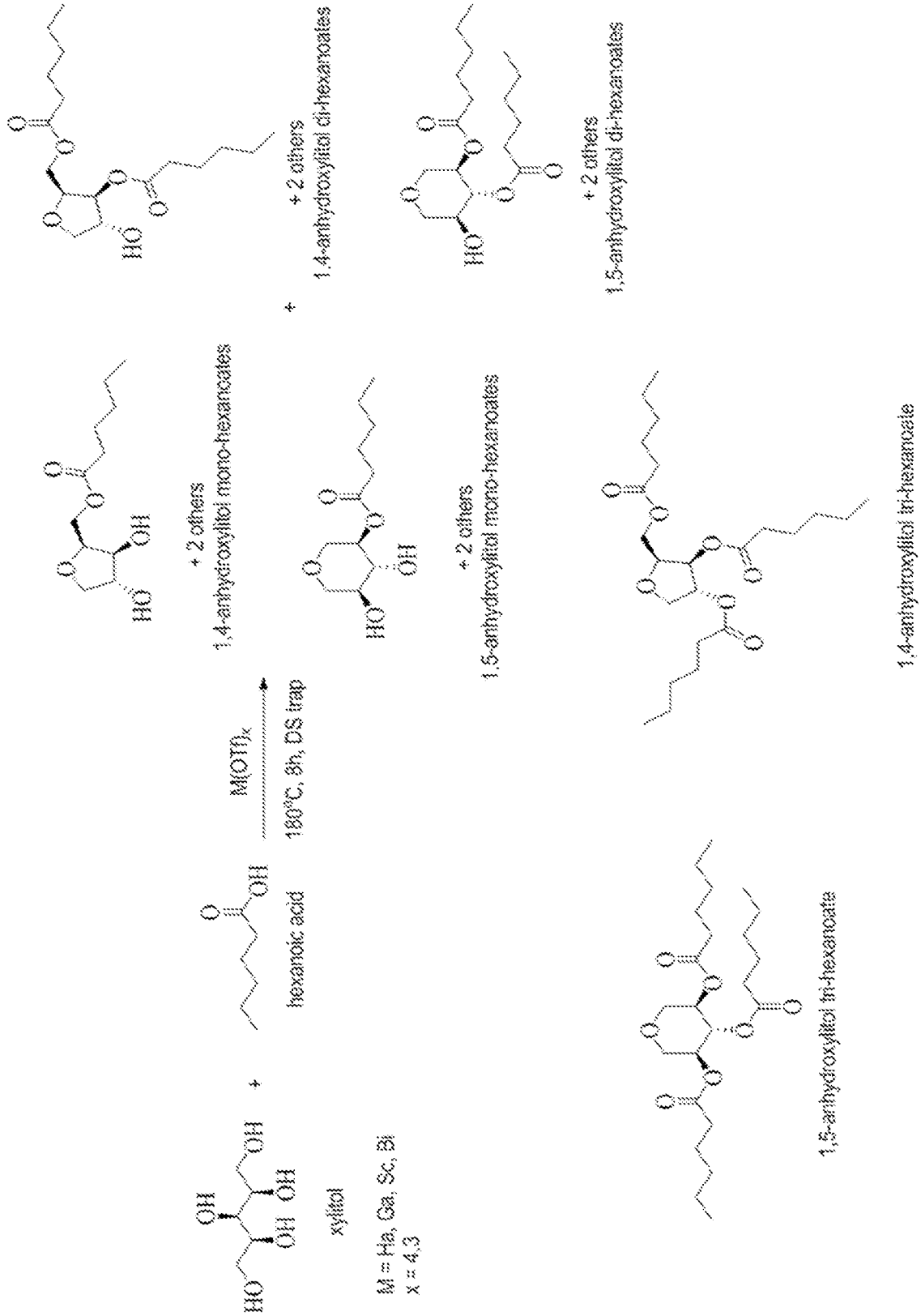

xylitol
M = Hf, Ga, Sc, Bi
x = 4,3
hexanoic acid
M(OTf)x
180°C, 8h, DS trap
1,4-anhydroxylitol mono-hexanoates
+ 2 others
1,5-anhydroxylitol mono-hexanoates
+ 2 others
1,4-anhydroxylitol di-hexanoates
+ 2 others
1,5-anhydroxylitol di-hexanoates
1,4-anhydroxylitol tri-hexanoate
1,5-anhydroxylitol tri-hexanoate

FIG. 3.

GC Analysis Results:

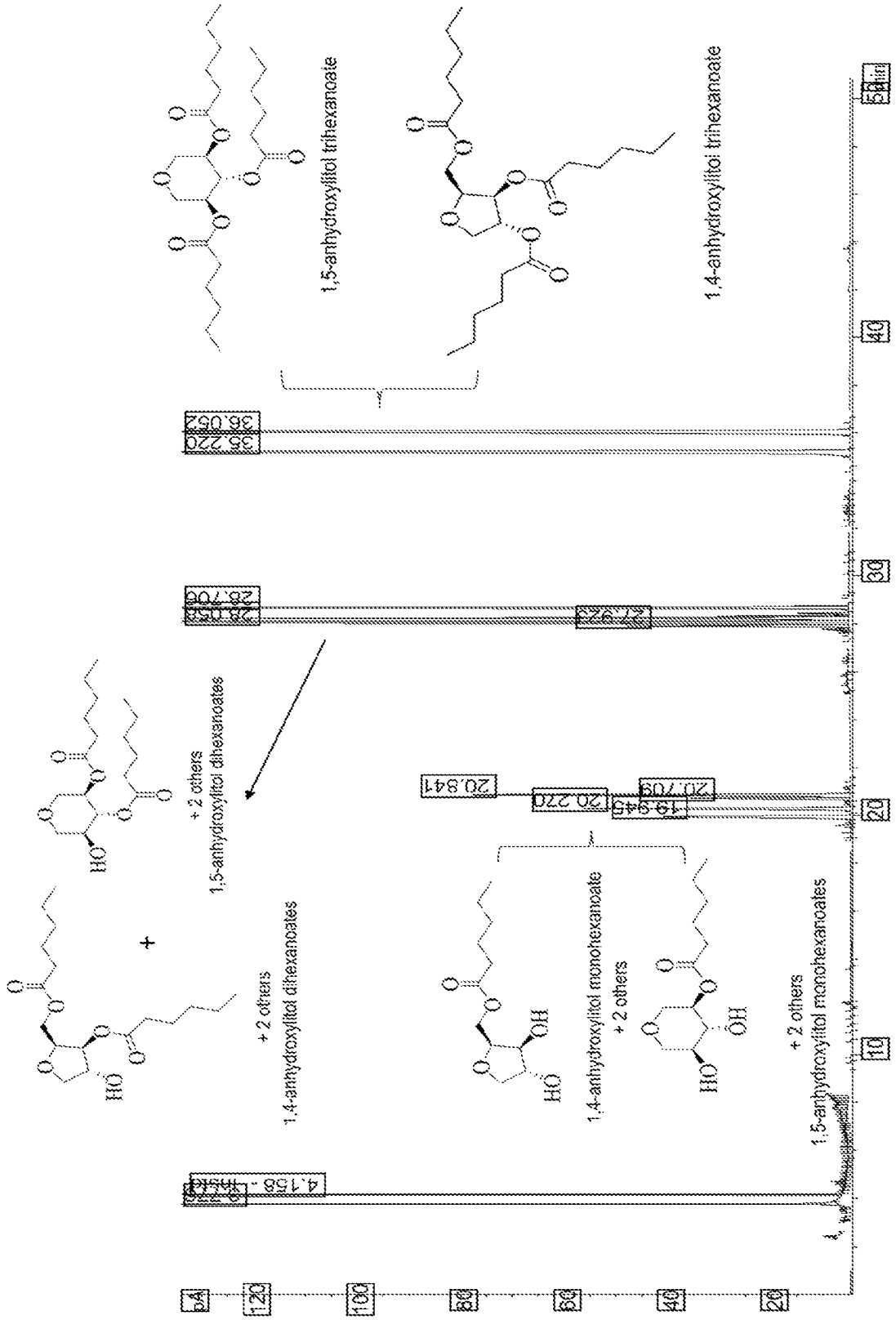


FIG. 4. GC Analysis Results:

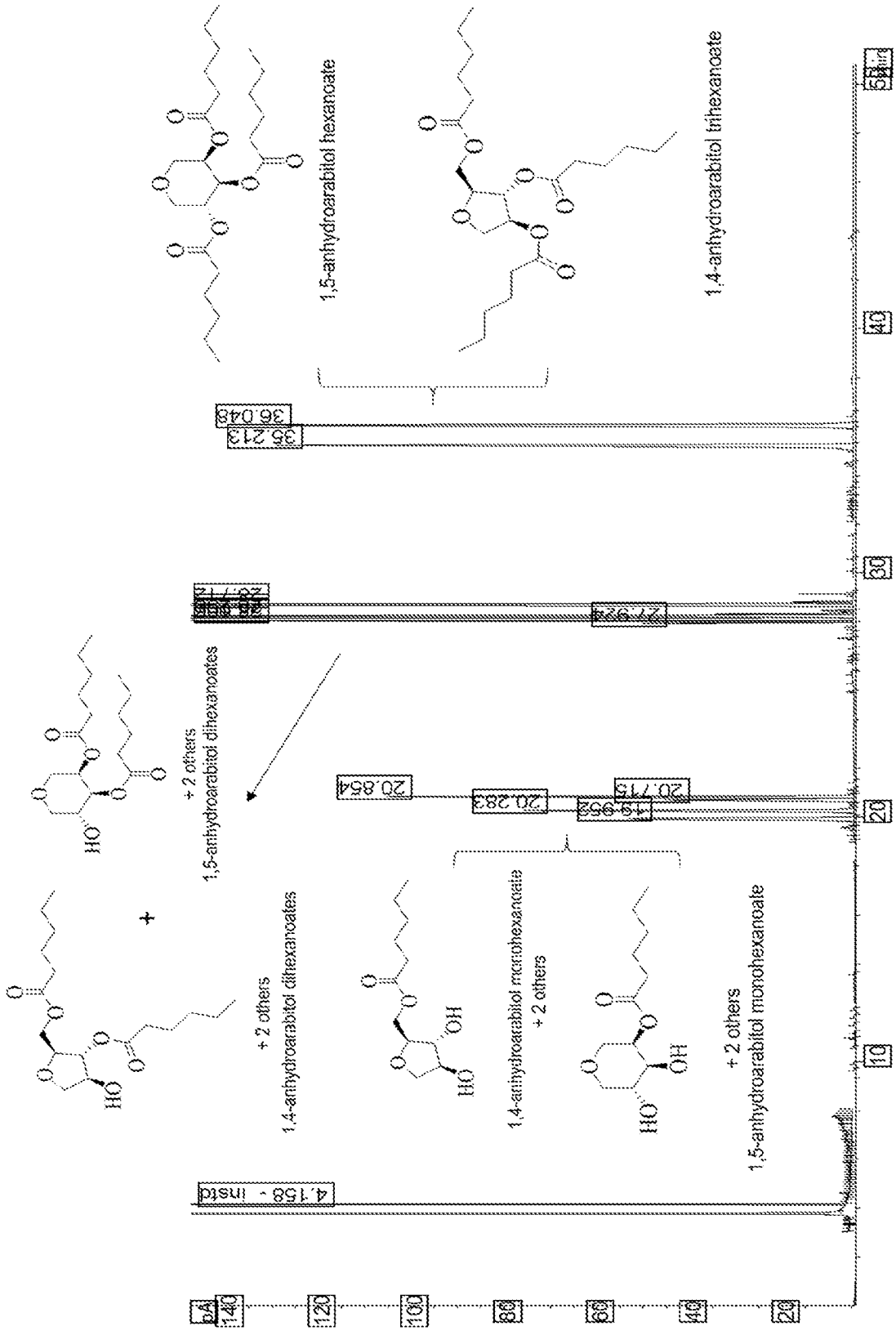
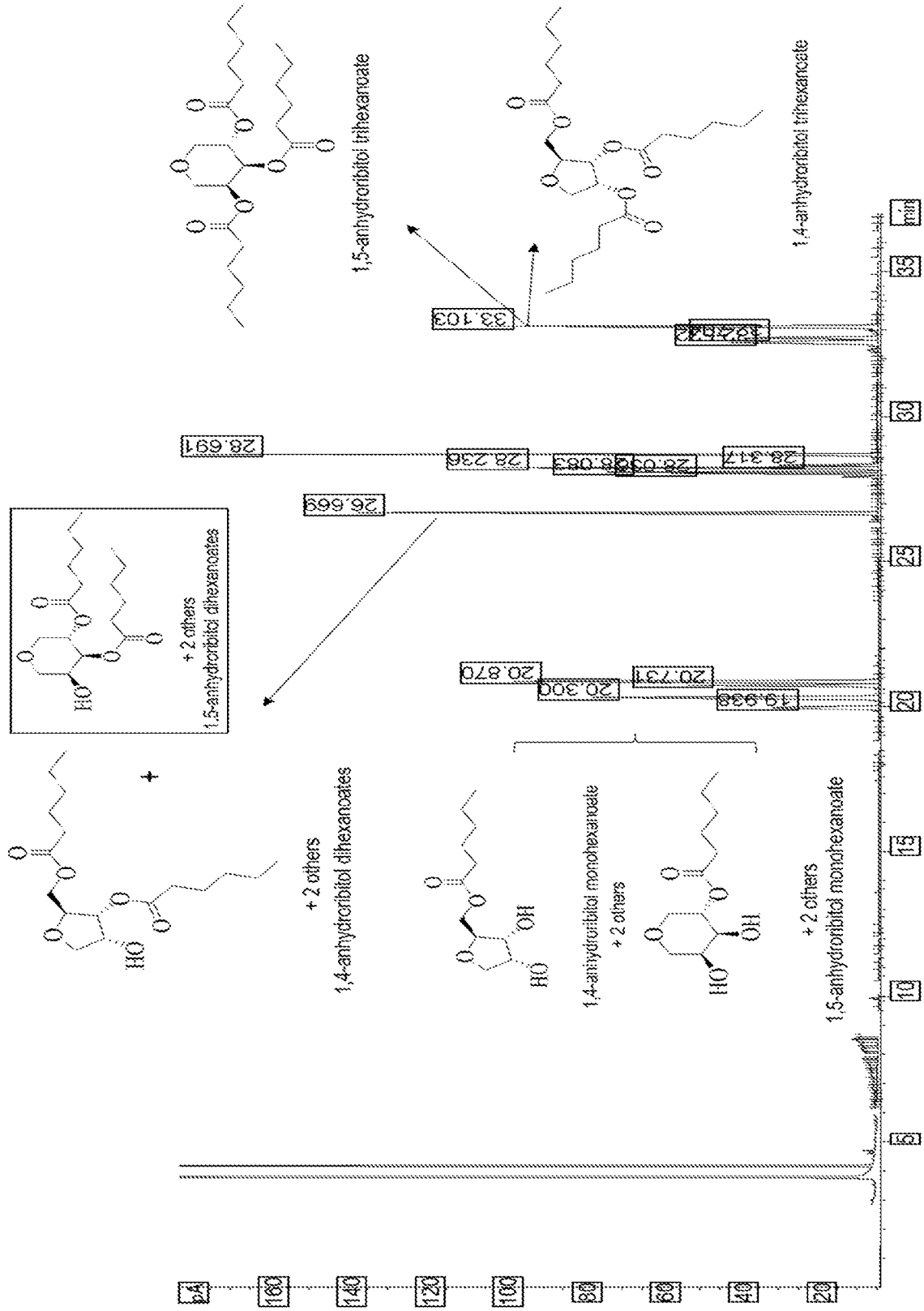


FIG. 5. GC Analysis Results:



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 16/65523

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 307/20; A61K 31/25 (2017.01)
CPC - C07D307/20; A61K31/25
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)
IPC(8): C07D 307/20; A61K 31/25 (2017.01)
CPC: C07D307/20; A61K31/25

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/548; 549/476; 549/478

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase, Google Scholar, PubWEST
anhydropentitol, 1,4-anhydroxylitol, 1,5-anhydroxylitol, 1,4-anhydroarabinitol, 2,5-anhydroarabinitol, and 1,4-anhydroribitol, ester, pentitol/D-ribitol/D-arabinitol/D-xylitol, water-tolerant Lewis acid, one-pot synthesis, triflate, hafnium/gallium/scandium/bismuth

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2012/0136070 A1 (SELIFONOV et al.) 31 May 2012 (31.05.2012) para [0041]-[0042], [0134]-[0142]	1-25
Y	WO 2015/094895 A1 (ARCHER DANIELS MIDLAND COMPANY) 25 June 2015 (25.06.2015) pg 1, ln 9-11; pg 4, ln 1-9; pg 6, ln 19-21, Scheme 1; pg 7, ln 27-33; Fig 2; pg 8, Table 1; pg 8, ln 20 to pg 9, ln 24	1-25
A	WO 2015/156839 A1 (ARCHER DANIELS MIDLAND COMPANY) 15 October 2015 (15.10.2015) Entire Document	1-25
A	WO 2014/137619 A1 (ARCHER DANIELS MIDLAND COMPANY) 12 September 2014 (12.09.2014) Entire Document	1-25
A	US 6,630,579 B2 (CHARI et al.) 07 October 2003 (07.10.2003) Fig 3	1-25
A	US 6,013,812 A (HAAS et al.) 11 January 2000 (11.01.2000) Entire Document	1-25

☐ 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
25 January 2017	02 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