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(54) **Title:** CONTROL OF COLOR-BODY FORMATION IN ISOHEXIDE ESTERIFICATION

FIG. 3
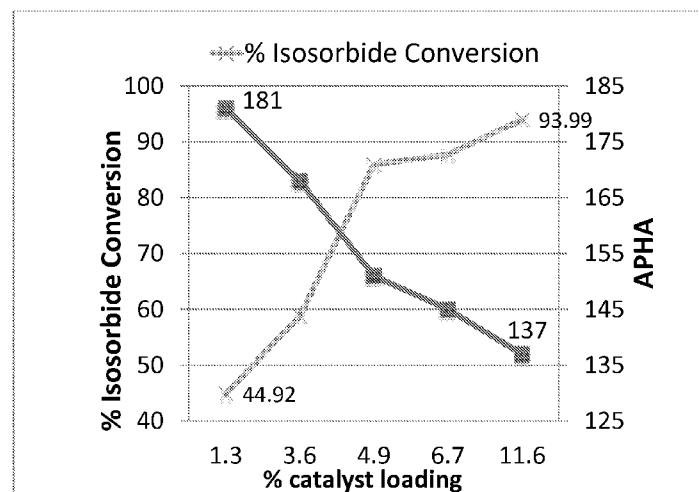
(57) **Abstract:** A method for preparing esters from isohexide compounds, and a means by which color bodies that may be made in situ during esterification of isohexide compounds are either prevented from forming or their amounts are minimized in the resultant product mixture are described.

WO 2015/094548 A1

CONTROL OF COLOR-BODY FORMATION IN ISOHEXIDE ESTERIFICATION

BENEFIT OF PRIORITY

The present application claims benefit of priority to U.S. Provisional Application Nos.:

5   61/917,390, filed on December 18, 2013, and 61/918,810, filed December 20, 2013, the contents of which are incorporated herein by reference.

FIELD OF INVENTION

The present disclosure relates to certain cyclic bi-functional materials that are useful as

10   monomers in polymer synthesis, as well as plasticizers, surfactants and intermediate chemical compounds. In particular, the present invention pertains to esters of 1,4:3,6-dianhydrohexitols and methods for their preparation.

BACKGROUND

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

20   produced from fossil, non-renewable sources.

One of the most abundant kinds of biologically-derived or renewable alternative feedstock for such materials is carbohydrates. Carbohydrates, however, are generally unsuited to current high temperature industrial processes. Compared to petroleum-based, hydrophobic aliphatic or aromatic feedstocks with a low degree of functionalization, carbohydrates such as sugars are complex, multi-

25   functionalized hydrophilic materials. As a consequence, researchers have sought to produce biologically-based chemicals that can be derived from carbohydrates, but which are less highly functionalized, including more stable bi-functional compounds, such as 2,5-furandicarboxylic acid (FDCA), levulinic acid, and 1,4:3,6-dianhydrohexitols.

1,4:3,6-Dianhydrohexitols (also referred to herein as isohexides) are derived from renewable

30   resources from cereal-based polysaccharides. Isohexides embody a class of bicyclic furanodiols that derive from the corresponding reduced sugar alcohols, for example depending on the chirality, D-sorbitol, D-mannitol, and D-iditol are dehydrated and cyclized to A) isosorbide, B) isomannide, and C) isoidide, respectively, the structures of which are illustrated in Scheme A.

35

Scheme A: A   B   C

isosorbide   isomannide   isoidide
from D-sorbitol   from D-mannitol   from D-iditol
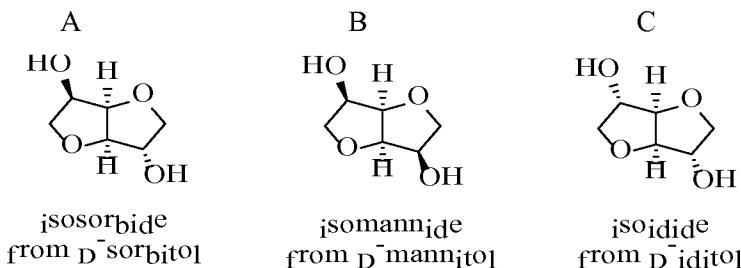
These molecular entities have received considerable interest and are recognized as valuable, organic chemical scaffolds for a variety of reasons. Some beneficial attributes include relative facility of their

5   preparation and purification, the inherent economy of the parent feedstocks used, owing not only to their renewable biomass origins, which affords great potential as surrogates for non-renewable petrochemicals, but perhaps most significantly the intrinsic chiral bi-functionalities that permit a virtually limitless expansion of derivatives to be designed and synthesized.

The isohexides are composed of two *cis*-fused tetrahydrofuran rings, nearly planar and V-

10   shaped with a 120° angle between rings. The hydroxyl groups are situated at carbons 2 and 5 and positioned on either inside or outside the V-shaped molecule. They are designated, respectively, as *endo* or *exo*. Isoidide has two *exo* hydroxyl groups, while the hydroxyl groups are both *endo* in isomannide, and one *exo* and one *endo* hydroxyl group in isosorbide. The presence of the *exo* substituents increases the stability of the cycle to which it is attached. Also *exo* and *endo* groups

15   exhibit different reactivities since they are more or less accessible depending on the steric requirements of the derivatizing reaction.

As interest in chemicals derived from natural resources increases, potential industrial applications have generated interest in the production and use of isohexides. For instance, in the field of polymeric materials, the industrial applications have included use of these diols to synthesize or

20   modify polycondensates. Their attractive features as monomers are linked to their rigidity, chirality, non-toxicity, and the fact that they are not derived from petroleum. For these reasons, the synthesis of high glass transition temperature polymers with good thermo-mechanical resistance and/or with special optical properties is possible. Also the innocuous character of the molecules opens the possibility of applications in packaging or medical devices. For instance, production of isosorbide at

25   a large industrial scale with a purity satisfying the requirements for polymer makers could be the basis for isosorbide to emerge as an important compound for industrial polymer applications. (*See e.g.*, F. Fenouillot *et al.*, "Polymers From Renewable 1,4:3,6-Dianhydrohexitols (Isosorbide, Isommanide and Isoidide): A Review," PROGRESS IN POLYMER SCIENCE, vol. 35, pp.578-622 (2010); or X. Feng *et al.*, "Sugar-based Chemicals for Environmentally sustainable Applications," CONTEMPORARY SCIENCE

30   OF POLYMERIC MATERIALS, Am. Chem. Society, Dec. 2010; or isosorbide-based plasticizers, e.g., U.S. Patent No. 6,395,810, contents of each are incorporated herein by reference.)

One of the common disadvantages with the use of isohexides to make ester derivatives is the tendency of the synthesis reactions to generate color-bodies as a side product or as a degradation of

byproduct compounds derived from reacting the isohexides. Typically, the color-bodies are formed at elevated temperatures, in the presence of oxygen. Given that esters manifest a multitude of utilities as plasticizers, dispersants, lubricants, flavoring agents, solvents, etc., and that isohexide esters are commonly used as plasticizers and polymers, and variants thereof are being aggressively synthesized and studied for enhanced performance in these realms *vis a vis* current materials, better process to synthesize product of greater purity with less color-bodies is desirable. A way to reduce the formation of color-bodies would help manufacturers produce a better quality and purer final product.

SUMMARY OF INVENTION

The present disclosure relates, in part, to a method for preparing esters from isohexide ester. Generally, the method involves reacting an isohexide and an organic acid, in the presence of a reducing Brønsted acid catalyst at a temperature up to about 250°C, for a time sufficient to produce the isohexide ester while limiting formation of color bodies in a product mixture to an APHA value of less than 230. The method further includes reducing incumbent color bodies or color-generating precursor compounds in a preparation of the isohexide or organic acid prior to reacting with the reducing Brønsted acid.

Additional features and advantages of the present purification 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.

BRIEF DESCRIPTION OF FIGURES

FIG. 1, depicts an exemplary synthesis of isosorbide esters according to an embodiment of the present method.

FIG. 2, shows a chromatogram of results obtained from quantitative analysis conducted by gas chromatography (GC) of isomers synthesized according to an embodiment of the present invention.

FIG. 3, is a graph showing the relationship between the percent catalyst load of phosphonic acid (H_3PO_3) and its impact on APHA values and percent conversion of isosorbide when reacted at 175°C, 7 hours.

FIG. 4, shows a series of photos of the respective degree of color attenuation in isohexide ester product mixtures that have been reacted with H_3PO_3 catalyst (175°C, 7h.), as compared to stock solution of 2-ethyl-hexanoic acid (2EH).

FIG. 5, shows photos of APHA color attenuation in isohexide product mixtures prepared from a pre-distilled solution of 2EH (APHA 6) using phosphonic acid catalyst loads of 1 wt.% and 5 wt.%, respectively at 205°C, 7 hours.

FIG. 6, are photos of the results of a high temperature thermal stress tests for about 10 g. of isosorbide product mixture, which was subjected to 200°C for 1 hour in air.

DETAILED DESCRIPTION OF THE INVENTION

Section I. – Description

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

Isohexide starting materials can be obtained by known methods of making respectively isosorbide, isomannide, or isoidide. Isosorbide and isomannide can be derived from the dehydration of the corresponding sugar alcohols, D-sorbitol and D mannitol. As a commercial product, isosorbide is also available easily from a manufacturer. The third isomer, isoidide, can be produced from L-idose, which rarely exists in nature and cannot be extracted from vegetal biomass. For this reason, researchers have been actively exploring different synthesis methodologies for isoidide. For example, the isoidide starting material can be prepared by epimerization from isosorbide. In L. W. Wright, J. D. Brandner, *J. Org. Chem.*, 1964, *29* (10), pp. 2979–2982, epimerization is induced by means of Ni catalysis, using nickel supported on diatomaceous earth. The reaction is conducted under relatively severe conditions, such as a temperature of 220°C to 240°C at a pressure of 150 atmosphere. The reaction reaches a steady state after about two hours, with an equilibrium mixture containing isoidide (57-60%), isosorbide (30-36%) and isomannide (5-7-8%). Comparable results were obtained when starting from isoidide or isomannide. Increasing the pH to 10-11 was found to have an accelerating effect, as well as increasing the temperature and nickel catalyst concentration. A similar disclosure can be found in U.S. Patent No. 3,023,223, which proposes to isomerize isosorbide or isomannide. More recently, P. Fuertes proposed a method for obtaining L-iditol (precursor for isoidide), by chromatographic fractionation of mixtures of L-iditol and L-sorbose (U.S. Patent Publication No. 2006/0096588; U.S. Patent No. 7,674,381 B2). L-iditol is prepared starting from sorbitol. In a first step sorbitol is converted by fermentation into L-sorbose, which is subsequently hydrogenated into a mixture of D-sorbitol and L-iditol. This mixture is then converted into a mixture of L-iditol and L-sorbose. After separation from the L-sorbose, the L-iditol can be converted into isoidide. Thus, sorbitol is converted into isoidide in a four-step reaction, in a yield of about 50%. (*See, e.g.,* International Patent Application WO13125950) The contents of the cited references are incorporated herein by reference.

A. Preparation of Isohexide Esters

Fischer-Speier esterification is the current standard protocol for industrial preparation of esters. Fischer-Speier esterification embodies a straightforward process for direct alcohol acylation with carboxylic acids employing Brønsted or Lewis acid catalysts. However, color is problematic when converting thermally sensitive substrates such as isohexides in the presence of strong acid catalysts. The desire is to minimize downstream processing unit operations by developing a catalyst that can furnish relatively high yields (e.g., ≥ 55%-60%) of target esters while minimizing color body formation or accretion.

In contrast to conventional commercial esterification protocols, which typically involve at least two operational steps – a synthesis reaction followed with purification or decolorization (e.g., crystallization, distillation and/or chromatography) of the product – the esterification method according to the present invention is simpler. The method involves a single-step operation. In the commercial realm, there is a desire to eliminate downstream processing entirely. Hence, a process that can make either product which is or approaches colorlessness (so-called "water-white"), or product that is within tolerable color specifications, in a single reaction without further need for later purification would be quite advantageous in terms of cost and efficiency.

For purposes of ascertaining acceptable levels of color in the product mixture, one employs the APHA color standard, named for the American Public Health Association and defined by ASTM D1209, incorporated herein by reference. (It was originally intended to describe the color of waste water, but its usage has expanded to include other industrial applications.) APHA is similar to the Hazen color scale test, which uses a platinum-cobalt (Pt/Co) solution, where the color of water could be used as a measure of concentration of dissolved and particulate material. Impurities can be deeply colored, for instance dissolved organic compounds such as tannins can result in dark brown colors. The APHA color scale is from 0 to 500, where 0 is colorless and 500 is the most colored.

A feature of the present invention is the ability to reduce or eliminate color bodies that may be made *in situ* during esterification of an isohexide compound. The color bodies are either prevented from forming or their amounts are minimized in the resultant product mixture. The method involves: reacting an isohexide and a carboxylic acid, in the presence of a reducing Brønsted acid catalyst for a time sufficient to yield a product mixture that exhibits an APHA value of less than 230. Typically, the product mixture exhibits an APHA value of ≤ 185, desirably the APHA value is ≤ 150.

The isohexide can be at least one of: isosorbide, isomannide, and isoiodide. The organic acid can be at least an alkanoic acid, alkenoic acid, alkynoic and aromatic acid, having C_2-C_{26}. The isohexide is transformed to a corresponding ester at a conversion rate of at least 40%, desirably the conversion rate is about 50% or greater.

The esterification is performed at a temperature in a range from about 150°C or 160°C to about 240°C or 250°C. Typically, the reaction temperature is in a range from about 170°C or 175°C to about 205°C or 220°C.

The reducing Brønsted acid catalyst is present in an amount of at least 0.5 wt.% relative to the amount of isohexide. In certain embodiments, when the amount of reducing Brønsted acid catalyst is > 5.0 wt. %, the product mixture contains predominantly diesters. In other embodiments, when the reducing Brønsted acid catalyst is present in an amount from about 2.5 wt. % to about 5.0 wt. %, the product mixture contains about a 1:1 ratio of monoesters and diesters. In still other embodiments, when the amount of reducing Brønsted acid catalyst is present in an amount < 2.5 wt. %, the product mixture contains predominantly monoesters.

Table 1, lists several conventional acid catalyst species that have commercial or potential value as comparative examples in terms of product color, catalyst load, and conversion rate relative to a reducing Brønsted acid. The methods described herein are exemplified by use of phosphonic acid (H_3PO_3) also known as phosphorus acid as the reducing Brønsted acid. In Table 1, the comparative examples tended to generate dark colored products with APHA values over 250.

Table 1. Catalyst, Catalyst Load, Percent (%) Isosorbide conversion, APHA Color Values

Catalyst	Loading (wt.% vs. isosorbide)	APHA	% isosorbide conversion
Autocatalysis	0.0	500	23.39
Sn(II)2EH	9.9	500	66.23
Sn(II)2EH	5.1	500	42.11
(butyl)$_2$SnCl$_2$	5.2	500	38.66
HaCl$_4$	5.4	500	52.83
(butyl)$_2$Sn(laurate)$_2$	5.1	306	35.28
ZrCl$_4$	5.4	500	42.16
ZrCl$_4$	5.1	500	47.98
(butyl)$_2$Sn(maleate)	5.3	319	38.48
SnCl$_4$	5.7	500	88.55
SnCl$_2$	5.7	277	87.99
BiCl$_3$	5.7	500	36.33
La(OTf)$_3$	1.0	500	82.49
Dibutyltin(IV)oxide	5.7	281	31.88
Fe(OTf)$_3$	1.0	500	69.91
Pre-reaction mixture		96	
Phosphorus acid	11.6	131	93.99
Phosphorus acid	6.7	145	83.73
Phosphorus acid	4.9	153	74.08
Phosphorus acid	3.6	168	58.79
Phosphorus acid	1.3	180	40.92
Phosphorus acid	0.6	196	28.43

Certain strong Brønsted or Lewis acid catalysts (e.g., H_2SO_4) will produce color-bodies. We have found that inclusion of a reducing Brønsted acid and one or more Brønsted and/or Lewis acid that effectuates high conversion of isosorbide to the corresponding mono and diesters of 2-

ethylhexanoic acid can also concomitantly mitigate the buildup of colored bodies in the product. The color tincture of the product mixture of the esterification decreases with an increase in concentration of the reducing Brønsted acid catalyst.

A particular reducing Brønsted acid species is phosphonic acid (H_3PO_3), also known as phosphorus acid, which is a crystalline solid, commercially available, inexpensive, and possesses a strong acidity (pKa ~1). This material evinces both high catalytic activity in the context of Fischer esterifications and pronounced color attenuation of the product mixture. To date, we believe that phosphonic acid has not received significant attention in this regard, either as a Brønsted acid in the catalysis of isohexide acylation with carboxylic acids, concerning color mitigation of products or concerning high isohexide conversions. Further, at this time, phosphonic acid is one that manifests both high reactivity and concomitant color diminution.

Hence, it was surprising to discover that, although a Brønsted acid, phosphonic acid not only helps to catalyze and increase the conversion rate to make esters from isohexides, but also can help reduce significantly the development of undesired color bodies in the product mixture when used in sufficient quantities (e.g., ≥ 1.0 wt.%; preferably ≥ 1.5 wt.% or 2.0 wt.%). Phosphonic acid manifests highly effective catalytic activity (~80%-95%) (i.e., efficacy similar to that exhibited for tin chlorides, ~87%-89%), in the esterification of isosorbide to mono and diesters of 2-ethylhexanoic acid, according to a particular embodiment.

Phosphonic acid proved to yield high isosorbide conversion to the corresponding mono- and diesters, while also displaying pronounced antioxidant properties that effectively controls and inhibits color body formation or accumulation in the product mixture.

Phosphonic acid functions as a catalyst for the acylation reaction, as well as provides a powerful reducing agent in solution that helps mitigate the formation of color bodies. Although not to be bound by theory, it is believed that the phosphonic acid may interact with color-body precursors to prevent their transition to colored entities. Scheme 1 illustrates one embodiment of the reaction. The reaction is performed neat.

Scheme 1. Phosphonic acid (H_3PO_3) catalyzed Fischer esterification of isosorbide to mono- and diesters of 2-ethylhexanoic acid (2EH).
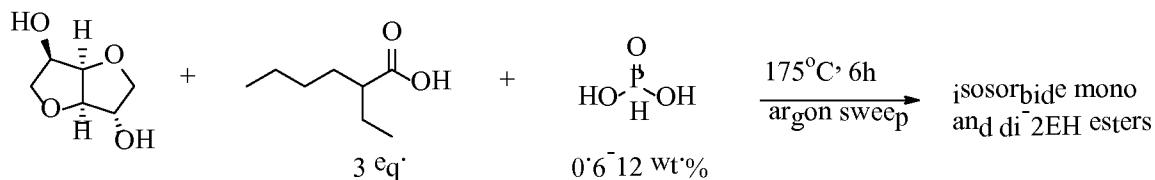
According to the present method, the conversion rate of isohexide to its corresponding esters is about least 40%-50%. Typically, the isohexide conversion rate is about 55% or greater, more typically about 65% or 70% or greater (e.g., about 75%, 80%, 84%, 87%, 90%, 92%, 95%, or greater).

While the method described herein are exemplified with 2-ethylhexanoic acid, the method is suitable for use with any organic acid desired for esterification with the isohexide, including alkanoic acid, alkenoic, and aromatic acids of C_2 to C_{26} in size, provided only that the organic acid is soluble in the reaction mixture.

Phosphonic acid is reported to decompose to phosphoric acid and phosphine at 200°C, and yet doesn't seem to adversely affect the esterification process/color body mitigation at this temperature, as demonstrated by results in Table 2, where isosorbide manifested complete conversion to the corresponding esters, primarily diesters, with minimal color accretion from reactions carried out at 205°C for 7h..

Table 2. H_3PO_3 Catalyzed Isosorbide Esterification with Distilled
2-Ethyl-Hexanoic Acid (2EH), 205°C, 7h.

Sample	Comparison	Loading (wt.% vs. isosorbide)	APHA (color)	% isosorbide conversion
1.	Pre-reaction mixture undistilled 2EH		96	
2.	Pre-reaction mixture distilled 2EH		6	
3.	Auto-catalysis	0	263	57 @ 5h
4.	Phosphonic Acid	1.20	136-138	85 @ 5h
5.	Phosphonic Acid	5.48	98	100 @ 5h

As part of the process to minimize color, one can either pre-purify the staring reagents, for example, by distilling the alkanoic acid (also may use alkenoic or alkynoic acids) before esterification or perform follow-on chromatography, among other purification techniques. The result of using phosphonic acid in the product mixture at a concentration of about 1 wt. % (APHA 136-138) and 5 wt.% (APHA 98), respectively, manifests relatively good color attenuation in comparison to the auto-catalysis value (APHA 263), and was much more closer in color to that of the clear distilled 2EH solution (APHA 6).

A unique feature of phosphonic acid is that it not only catalyzes the reaction, but has propitious reducing agent potential, and thus can further oxidize to phosphoric acid. In the area of isohexide esterification, phosphonic acid is the only catalyst of those screened to date, that discerns both high isosorbide conversion and color mitigation. Furthermore, no literature precedent for such behavior (aggressive catalysis, color mediation) was distinguished.

Others have used hypophosphorus acid (H_3PO_2), an aqueous solution. The kinetics of the reaction may be similar to that of the hypophosphorus and phosphonic acid as each has pKa near 1. Comparative catalyses for these acids, however, suggest that the chemistry that each of the acids display in mitigating color are likely dissimilar. Hypophosphorus acid degrades at 130°C, and can be obtained only as a 50% aqueous solution, which because of the presence of water would not function in a similar manner as phosphonic acid in the present reaction system.

As an exemplary method, the present synthesis protocol for acid-catalyzed esterification of isohexides (e.g., isosorbide) with an carboxylic acid (e.g., 2-ethylhexanoic acid) involves: A three-neck, 500 mL round bottomed flask equipped with a tapered, PTFE coated magnetic stir bar is charged with 50 g of isosorbide (0.342 mol), 148 g of 2-ethylhexanoic acid (1.026 mol) and 5 wt.%

5   acid catalyst (relative to isosorbide). The necks of the flask are fitted with a Dean-Stark trap, argon line, and a rubber septum centrally pierced by a stainless steel thermocouple. The flask is immersed in an oil bath and heated to 175°C with a concurrent, vigorous argon sweep. Aliquots are pulled each hour and analyzed by gas chromatography. The reaction is halted at 7 hours. Figure 1 illustrates an embodiment of the present method for synthesizing isosorbide 2EH monoesters.

10   Figure 2, is a representative chromatogram of the results obtained from quantitative analysis conducted by gas chromatography (GC) of the two sets of four isomers synthesized according to the reaction above.

Interplay of three factors – catalyst load, temperature, and time – appears to facilitate the operation of the esterification reaction to yield low amounts of color bodies, which leads to a clearer

15   product and minimizes a need for downstream purifications. Counterintuitive to conventional observations in which an acid catalyst at greater amounts tend to generate more color bodies, one of the advantages and unexpected results of using phosphonic acid is that as the catalyst load of acid increases manifestation of color-bodies tends to decrease. Figure 3, is a graph showing the relationship between the percent catalyst load of phosphonic acid (H_3PO_3) and its impact on APHA

20   values and percent conversion of isosorbide when reacted at 175°C, 7 hours. As the acid catalyst concentration increases from 1.3 wt.% to 11.6 wt.%, the APHA color value of the product mixture decreases from 181 to 137, and the conversion rate increases from about 45% to about 94%.

Figure 4, shows several photos of isosorbide product that have undergone acylation according to the present process. The accompanying photos highlight the dual role catalytic and oxygen

25   scavenging effect of phosphonic acid. In comparison to the stock 2-ethylhyexanoic acid *A*, with APHA tintometer value of 96, product mixture samples reacted (at 175°C for 7h) with phosphonic acid at 1 wt.% *B*, 2.5 wt.% *C*, 5 wt.% *D*, and 10 wt.% *E* catalyst load, respectively, show decreased color (APHA value of 192, 175, 145, and 137, respectively), while increased conversion yields of isosorbide from 43.56%, 55.22%, 86.52%, to 99.39%, respectively. In other words, with greater

30   amounts of catalysts one can achieve greater yield or conversion of the isohexide while still maintaining a clear solution with good color quality with APHA value of less than about 200. Test results for this phenomenon are summarized in Tables 1 and 3, which were reacted at 205°C and 175°C, respectively, for 7 hours.

35   Table 3. H_3PO_3 Catalysis Results: 2-Ethyl-Hexanoic Acid Esterification with Isosorbide, 175°C, 7h.

Sample	Loading (wt.% vs. isosorbide)	APHA (color)	% Isosorbide conversion	Exo/Endo (mean)	Exo/Endo (std. dev)	%CV
1.	0	96				

Comp.						
2.	11.6	137	93.99	4.05	0.07	1.59
3.	6.7	145	87.73	3.95	0.08	2.02
4.	4.9	151	85.92	4.09	0.08	2.02
5.	3.6	168	58.79	4.02	0.10	2.37
6.	1.3	181	44.92	3.96	0.08	2.00

N.B.: Product mixture from samples of catalysts typically used manifest APHA > 275.

Additionally, as results in Table 3, suggest that phosphonic acid exhibits greater regioselectivity for the exo-OH over the endo-OH of an isohexide molecule in a ratio of about 4:1.

Figure 5, are photos that show the decrease in APHA color value in isohexide product mixtures associated with an increase in phosphonic acid catalyst load of 1 wt.% and 5 wt.%, respectively (APHA 136, 98), as compared to a pre-distilled solution of 2EH (APHA 6) at 205°C, 7 hours.

Figure 6, shows photos of the results of high temperature thermal stress tests to explore the oxygen scavenging potential of the acid catalyst for mitigating color. The test sample contains about 10 g. of isosorbide product mixture, which was subjected to 200°C for 1 hour in air. The results suggest a window of good oxygen-scavenging performance and/or ability to incapacitate colored body precursors generated from thermal oxidiative decomposition of isosorbide in terms of the amount of phosphonic acid added to the isosorbide mixture. An isosorbide product sample that contains no phosphonic acid exhibits very light clear color (APHA ~76), while at phosphonic acid amounts of about 90,000 ppm (900 mg) the solution exhibits a deep dark color (APHA 500). At phosphonic acid loads of about 100 ppm, 300 ppm, 1000 ppm, respectively, the color of the solution lightens with increasing concentration (APHA > 500, 278, 191, 158, respectively). However, at a concentration of about 40,000 ppm (400 mg), the color of the solution darkens (APHA 465) again. This suggests that the window has a lower and upper limit for the amount of phosphonic acid between about 2,000 ppm (0.2 wt.%) (APHA 98) to about 5,000 ppm (0.5 wt.%) or about 10,000 ppm (1.0 wt.%) that is effective at maintaining control of color body development to a relatively low level, at an APHA value between about 76 and about 105.

Table 4, Phosphonic Acid-Catalyzed Esterification of Isohexides with 2-Ethyl-Hexanoic Acid

Isohexide	Catalyst Loading (wt.% v. isohexide)	APHA (neat, tintometer)	Percent (%) isohexide conversion	
Isosorbide	4.9	151	85.92	
Isomannide	5.3	210	75.27	
Isoiodide*	5.2	187	99.69	

*~80% purity, THF saturated

With regard to the three particular isohexides presented in Table 4, isosorbide (APHA 151) shows the best performance when reacted using phosphonic acid catalyst, with better color attenuation relative to either isoiodide (APHA187) or isomannide (APHA 210). This may be a result of the

nature of isomannide and isoidide. Isomannide is much more thermo-oxidatively unstable than isososorbide. Nonetheless, an APHA value of 210 for isomannide is far lower color production than typical. Normally, when isomannide is esterified with conventional catalyst the product would manifest an APHA color value of well over 500. In another example, isomannide reacts with 7.6
5   wt.% phosphonic acid (vs. isomannide), and yields 89.44% isomannide conversion over 7 hours at 175°C (APHA 210). The particular isoiodide sample shown in the Table is about 80% pure, containing a significant amount of THF, which is a species that is readily susceptible to thermo-oxidative decomposition, and hence generation of color bodies. We believe that for an isoiodide sample of greater purity (e.g., near 100% purity) one will see a greater reduction in color than that
10   indicated. The isoiodide product would have coloration comparable to or better than that of the isosorbide sample.

Polyesters can be made from the isohexide esters (e.g., isosorbide esters) having an APHA value of ≤ 150 prepared according to the present method. Hence, one can employ a method of making a polyester by obtaining an isohexide ester monomer made according to the methods
15   described herein, and polymerizing said isohexide ester monomer alone or with an additional monomer.

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

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CLAIMS

We claim:

1. A method for preparing an isohexide ester, comprising: reacting an isohexide and an organic acid, in the presence of a reducing Brønsted acid catalyst at a temperature up to about 250°C, for a time sufficient to produce the isohexide ester while limiting formation of color bodies in a product mixture to an APHA value of ≤ 185.

2. The method according to claim 1, further comprising reducing color bodies or color-generating precursor compounds in a preparation of the isohexide or organic acid prior to reacting with the reducing Brønsted acid.

3. The method according to claim 2, wherein reducing color bodies or precursor compounds is done by purifying the organic acid by at least one of chromatography, crystallization, or distillation.

4. A method for preparing an isohexide ester, comprising: contacting an isohexide and an acid with a reducing Brønsted acid catalyst for a time sufficient to yield a product mixture that exhibits an APHA value of less than 230, and wherein said isohexide is transformed to the isohexide ester at a conversion rate of at least 40%.

5. The method according to either claim 1 or 4, wherein said isohexide is at least one of: isosorbide, isomannide, and isoiodide.

6. The method according to either claim 1 or 4, wherein said acid is at least one of an alkanoic acid, alkenoic acid, and aromatic acid, having C_2-C_{26}.

7. The method according to claim 6, wherein said acid is 2-ethylhexanoic acid.

8. The method according to either claim 1 or 4, wherein said reducing Brønsted acid catalyst is phosphonic acid (H_3PO_3).

9. The method according to claim 1 or 4, wherein said product mixture exhibits an APHA value of ≤ 150.

10. The method according to claim 4, wherein said conversion rate is about 50% or greater.

11. The method according to claim 4, wherein said conversion rate is about 70% or greater.

12. The method according to claim 1 or 4, wherein said reducing Brønsted acid catalyst is present in an amount > 5.0 wt. % of a reaction mixture of said isohexide and organic acid.

13. The method according to claim1 or 4, wherein said reducing Brønsted acid catalyst is present in an amount from about 2.5 wt. % to about 5.0 wt. % of a reaction mixture of said isohexide and organic acid.

14. The method according to claim 1 or 4, wherein said reducing Brønsted acid catalyst is present in an amount < 2.5 wt. % of a reaction mixture of said isohexide and organic acid.

15. The method according to claim 12, wherein said product mixture contains predominantly diesters.

16. The method according to claim 13, wherein said product mixture contains about a 1:1 ratio of monoesters and diesters.

17. The method according to claim 14, wherein said product mixture contains predominantly monoesters.

18. An ester product mixture containing an isohexide ester and a reducing Brønsted acid, wherein said ester product mixture is formed from an isohexide and an acid, using the reducing Brønsted acid catalyst at a temperature in a range from about 150°C to about 250°C, and wherein said product mixture exhibits an APHA value of less than 230.

19. The ester product mixture formed according to claim 18, wherein said APHA value is ≤ 180.

20. The ester product mixture formed according to claim 18, wherein said reducing Brønsted acid catalyst is phosphonic acid (H_3PO_3).

21. A method of making a polyester comprising, obtaining an isohexide ester monomer made according to the method of claim 1 or 4, and polymerizing said isohexide ester monomer alone or with an additional monomer.

FIG. 1

Mono-2EH esters:
Enantiomer sets labeled as **a** and **b**

Di-2EH esters:
Enantiomer sets labeled as **c** and **d**

FIG. 2

FIG. 3

FIG. 4

A

Stock 2EH

APHA 96
measured x3
tintometer

B

1.0 wt. % H$_3$PO$_3$

APHA 192
43% isosorbide
conversion

C

2.5 wt. % H$_3$PO$_3$

APHA 175
55.22% isosorbide
conversion

D

5 wt. % H$_3$PO$_3$

APHA 145
86.52% isosorbide
conversion

E

10 wt. % H$_3$PO$_3$

APHA 137
99.39% isosorbide
conversion

FIG. 5

Distilled 2EH

Radial Head, 100°C, < 5 torr

APHA 6

A

5 wt.% H_3PO_3

100% conversion @ 5 h.

APHA 98

B

1 wt.% H_3PO_3

85% conversion

APHA 136

C
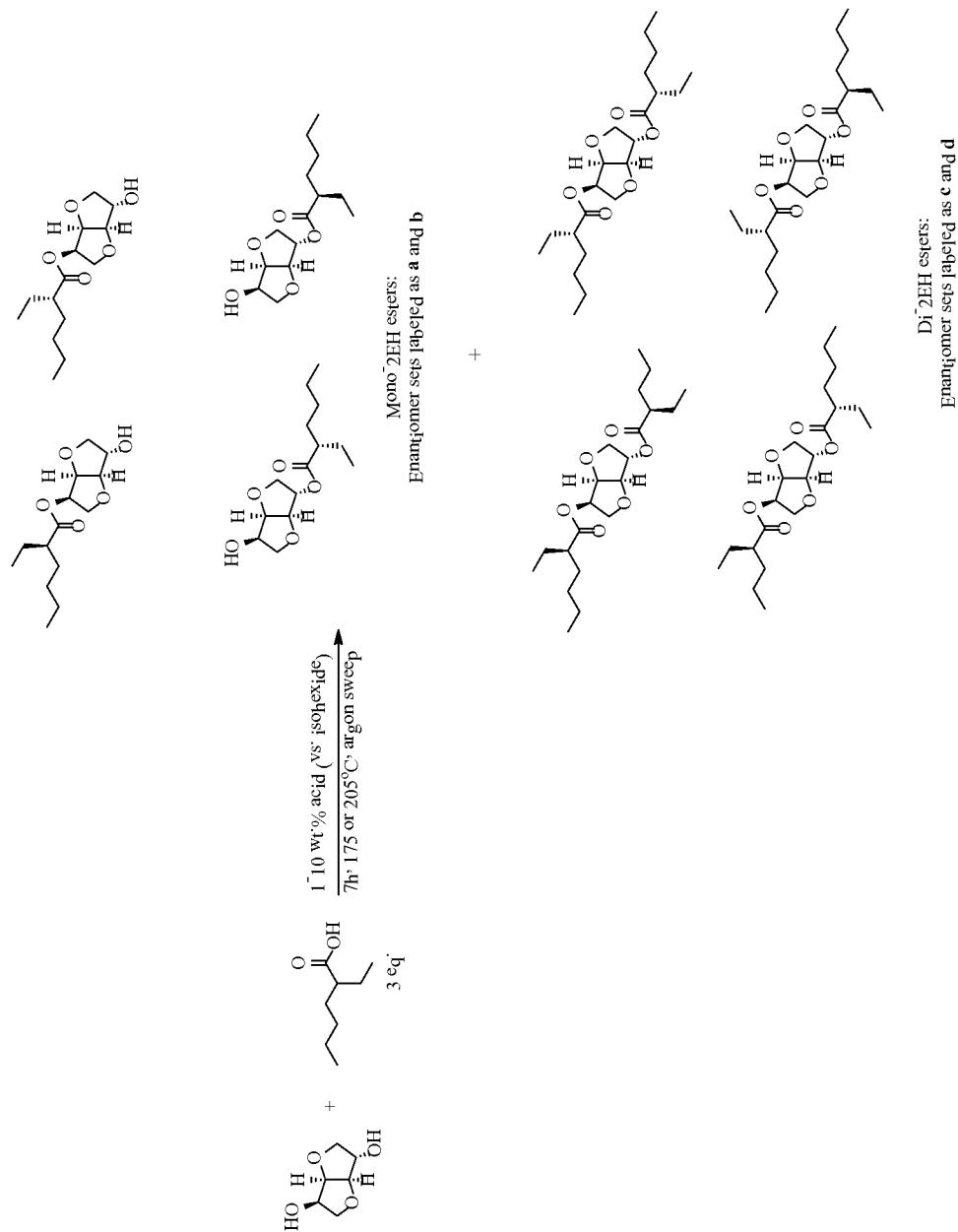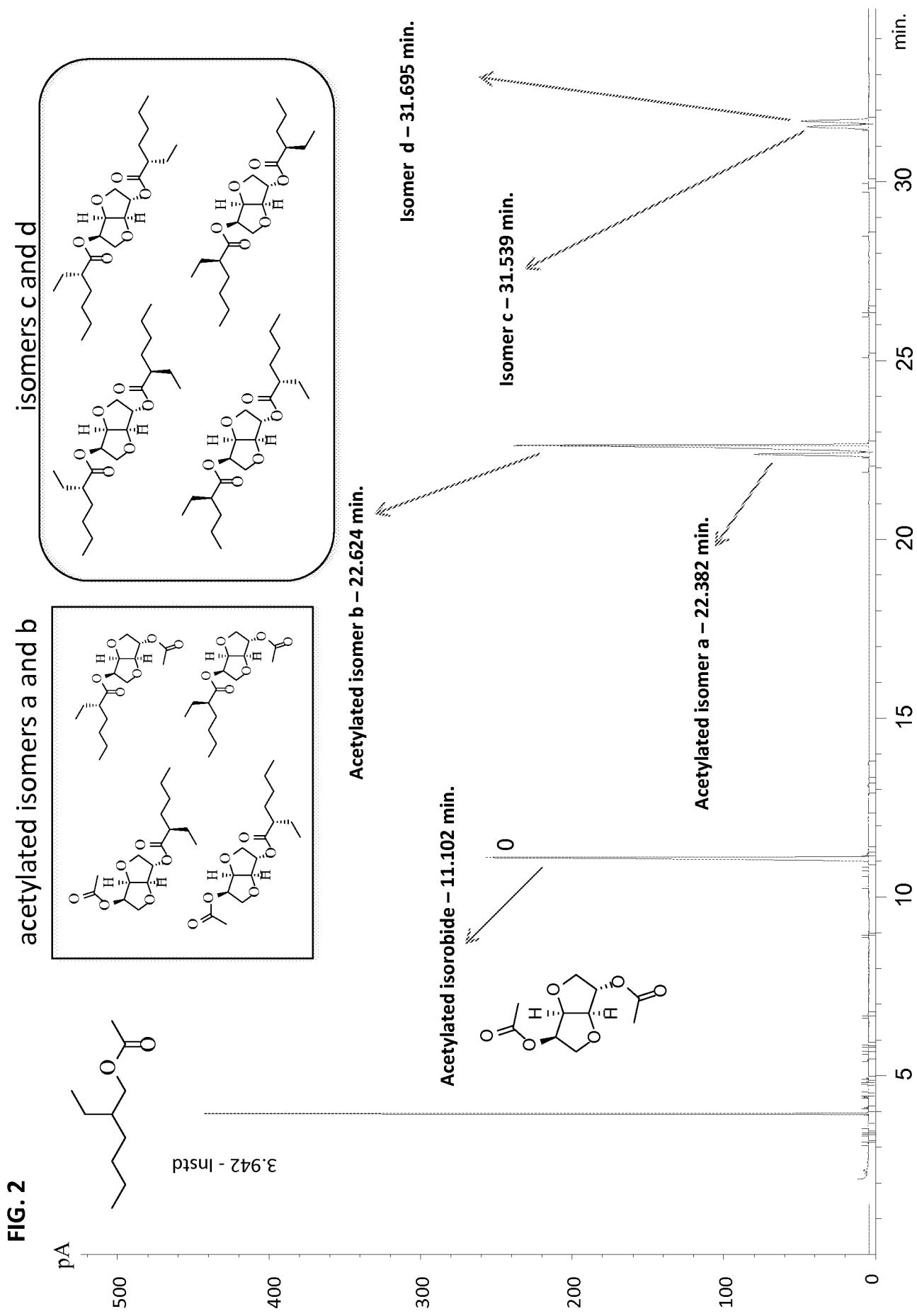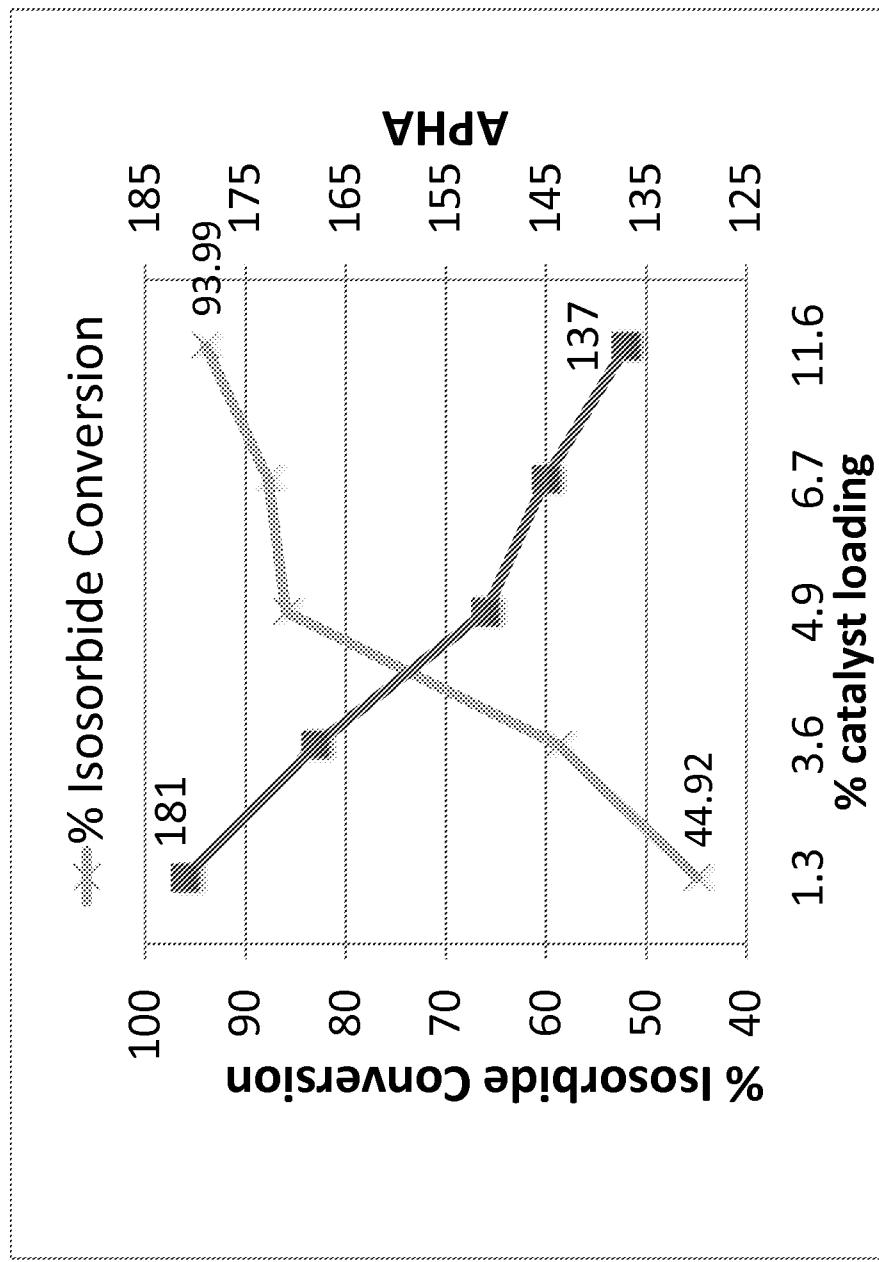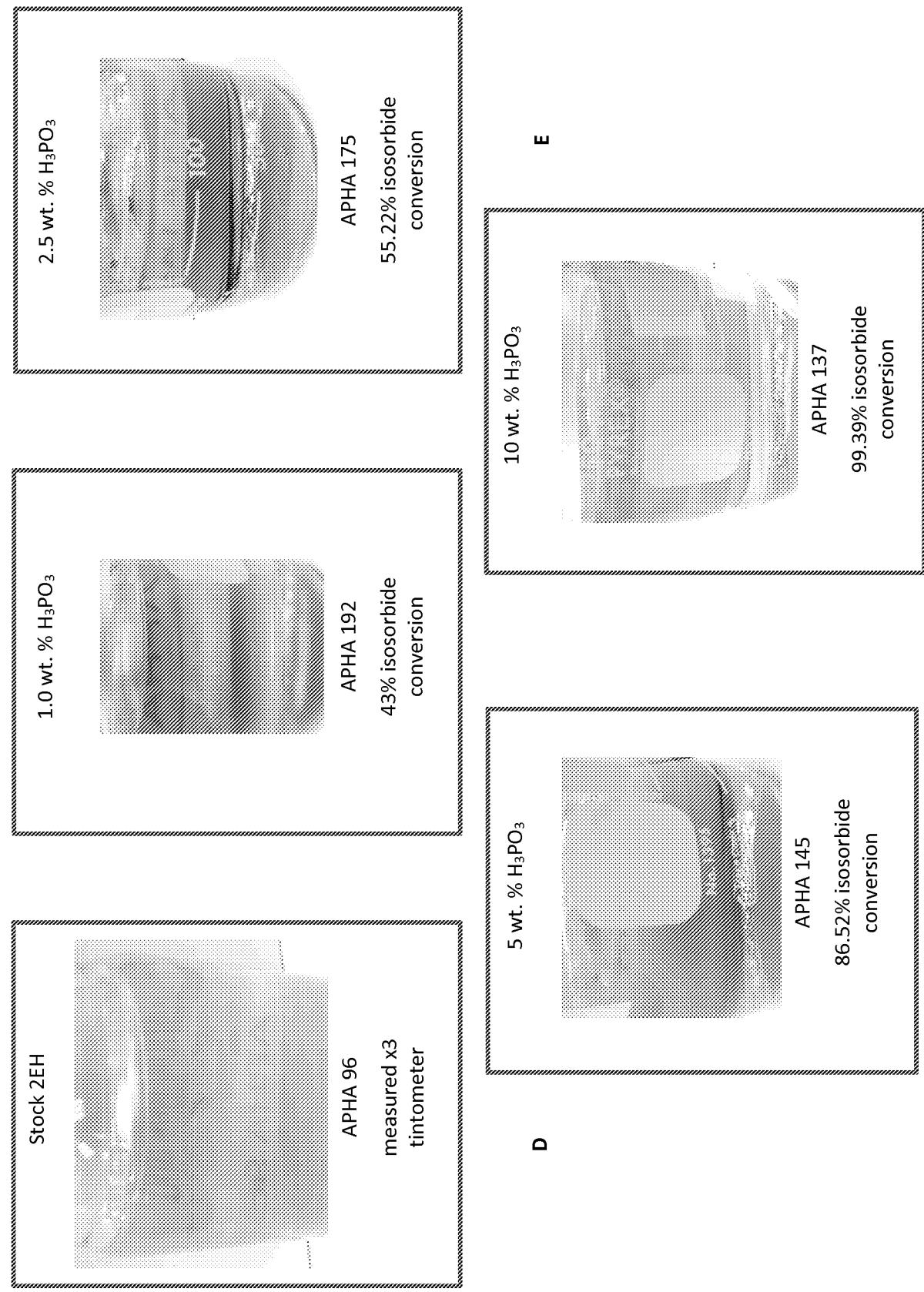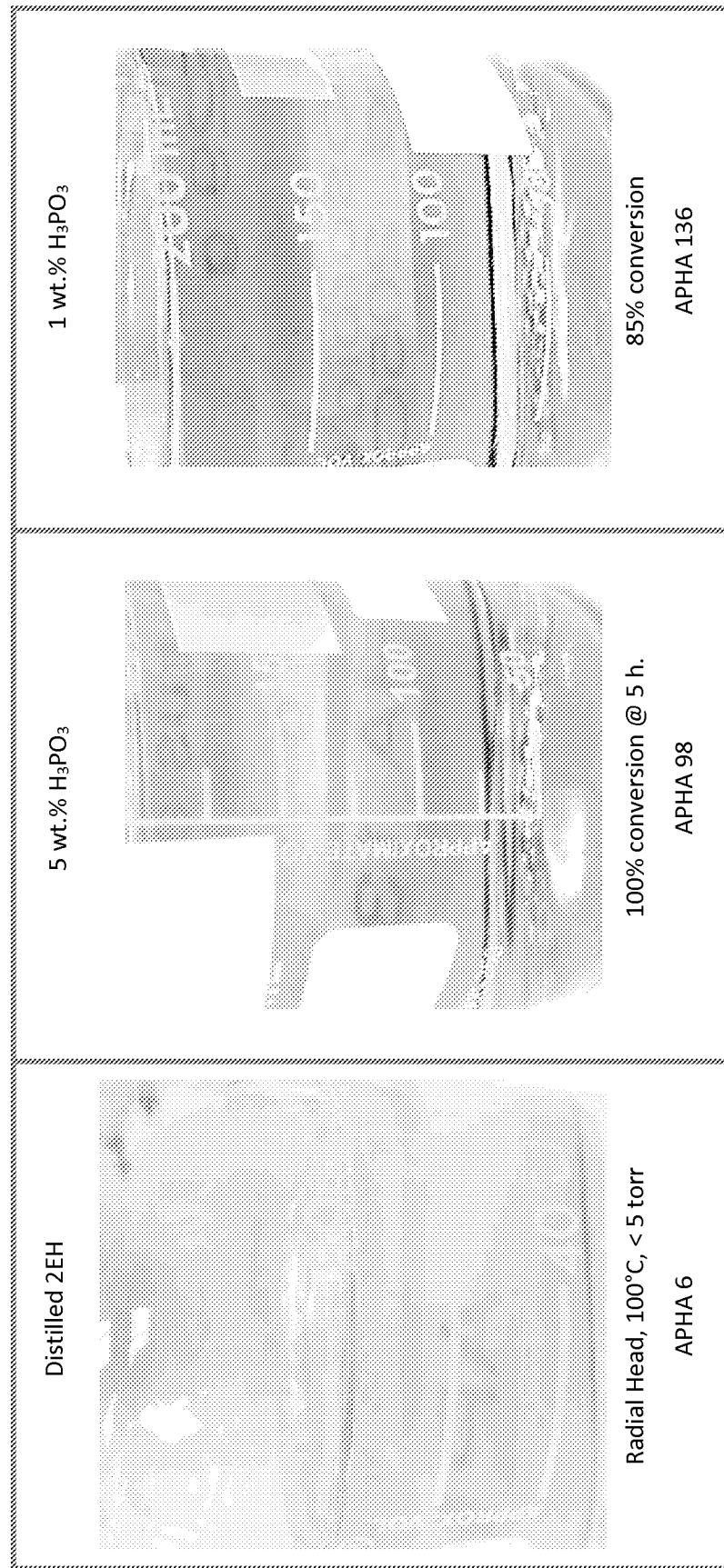
FIG. 6
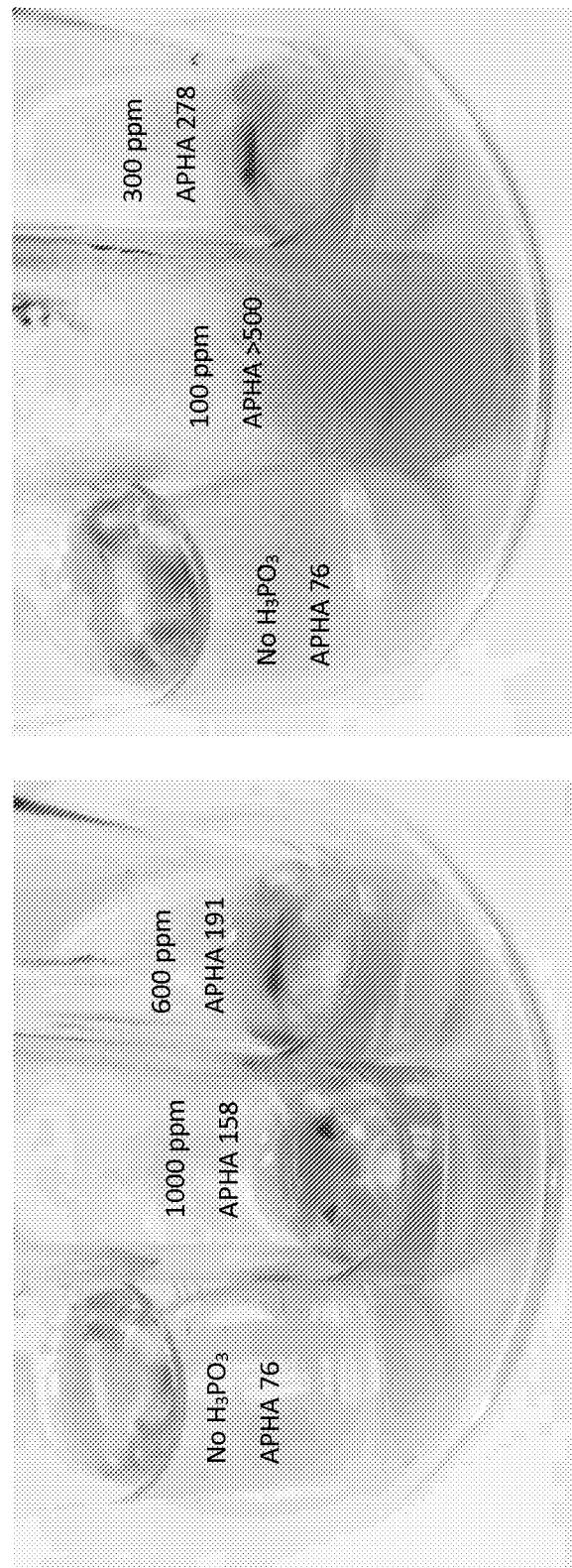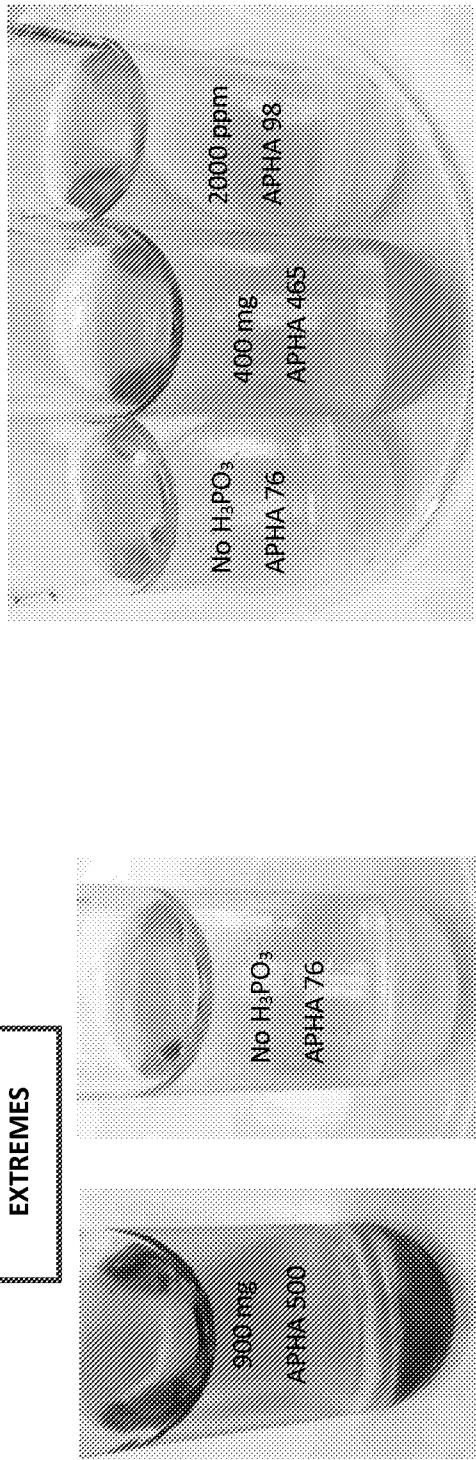
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - C07D 493/04 (2015.01)
CPC - C07D 493/04 (2014.11)
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 493/04; C08K 5/1535; C09F 1/04; C11D 3/20 (2015.01)
CPC - C07D 493/04; C08K 5/1535; C09F 1/04; C11D 3/20 (2014.11) (keyword delimited)
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC - 510/220; 524/109; 530/213; 549/464 (keyword delimited)
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Orbit, Google Patents, Google.
Search terms used: Isohexide, isosorbide, dianhydrohexitol, ester, APHA.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X ----	WO 2012/175237 A1 (EVONIK OXENO GMBH) 27 December 2012 (27.12.2012) See machine translation	1-6, 9-11, 14, 18, 19 ---------------------------------
Y		7, 8, 12, 13, 15-17, 20, 21
Y	US 8,609,872 B2 (FUERTES et al) 17 December 2013 (17.12.2013) entire document	7, 12, 13, 15-17
Y	4,690,783 A (JOHNSON JR) 01 September 1987 (01.09.1987) entire document	8, 20
Y	US 2012/0035090 A1 (BREFFA et al) 09 February 2012 (09.02.2012) entire document	16, 17
Y	BERSOT et al. Efficiency Increase of Poly(ethylene terephthalate-co-isosorbide terephthalate) Synthesis using Bimetallic Catalytic Systems. Macromol. Chem. Phys. 212: 2114-2120, 2011. [retrieved on 08.01.2015] Retreived from the Internet. <URL: http://www.readcube.com/articles/10.1002%2Fmacp.201100146? r3_referer=wol&tracking_action=preview_click&show_checkout=1>. page 2114	21

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

* Special categories of cited documents:	"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
"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	"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
"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)	"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
"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	"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 January 2015	**2 3 FEB 2015**

Name and mailing address of the ISA/US	Authorized officer:
Mail Stop PCT, Attn: ISA/US, Commissioner for Patents	Blaine R. Copenheaver
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	PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (July 2009)

（54）发明名称
控制异己糖醇酯化中颜色体形成

（57）摘要
描述了一种用于从异己糖醇化合物制备酯的方法，以及一种手段，通过该手段可以使在异己糖醇化合物的酯化过程中原位制造的颜色体被阻止形成亦或使它们的量在所得产物混合物中最小化。
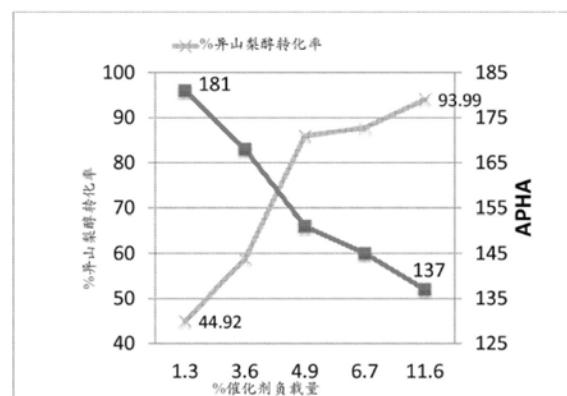
1. 一种用于制备异己糖醇酯的方法,包括:使一种异己糖醇和一种有机酸、在一种还原布朗斯台德酸催化剂存在下在最高达约250℃的温度下反应,持续一段足以产生该异己糖醇酯的时间同时将一种产物混合物中的颜色体的形成限制为≤185的APHA值。

2. 根据权利要求1所述的方法,进一步包括在与该还原布朗斯台德酸反应之前在制备该异己糖醇或有机酸中减少颜色体或颜色产生前体化合物。

3. 根据权利要求2所述的方法,其中减少颜色体或前体化合物是通过经由色谱法、结晶、或蒸馏中的至少一种纯化该有机酸完成的。

4. 一种用于制备异己糖醇酯的方法,包括:使一种异己糖醇和一种酸与一种还原布朗斯台德酸催化剂接触持续一段足以产生一种产物混合物的时间,该产物混合物展示出小于230的APHA值,并且其中所述异己糖醇以至少40%的转化率被转化为该异己糖醇酯。

5. 根据权利要求1或4中任一项所述的方法,其中所述异己糖醇是异山梨醇、异甘露糖醇、以及异艾杜糖醇中的至少一种。

6. 根据权利要求1或4中任一项所述的方法,其中所述酸是具有C_2-C_{26}的链烷酸、链烯酸、和芳香族酸中的至少一种。

7. 根据权利要求6所述的方法,其中所述酸是2-乙基己酸。

8. 根据权利要求1或4中任一项所述的方法,其中所述还原布朗斯台德酸催化剂是膦酸(H_3PO_3)。

9. 根据权利要求1或4所述的方法,其中所述产物混合物展示出≤150的APHA值。

10. 根据权利要求4所述的方法,其中所述转化率是约50%或更大。

11. 根据权利要求4所述的方法,其中所述转化率是约70%或更大。

12. 根据权利要求1或4所述的方法,其中所述还原布朗斯台德酸催化剂以所述异己糖醇和有机酸的反应混合物的>5.0wt.%的量存在。

13. 根据权利要求1或4所述的方法,其中所述还原布朗斯台德酸催化剂以所述异己糖醇和有机酸的反应混合物的从约2.5wt.%至约5.0wt.%的量存在。

14. 根据权利要求1或4所述的方法,其中所述还原布朗斯台德酸催化剂以所述异己糖醇和有机酸的反应混合物的<2.5wt.%的量存在。

15. 根据权利要求12所述的方法,其中所述产物混合物主要包含二酯。

16. 根据权利要求13所述的方法,其中所述产物混合物包含约1:1比率的单酯和二酯。

17. 根据权利要求14所述的方法,其中所述产物混合物主要包含单酯。

18. 一种包含异己糖醇酯和还原布朗斯台德酸的酯产物混合物,其中所述酯产物混合物是从一种异己糖醇和一种酸、使用该还原布朗斯台德酸催化剂在从约150℃至约250℃的范围内的温度下形成的,并且其中所述产物混合物展示出小于230的APHA值。

19. 根据权利要求18形成的酯产物混合物,其中所述APHA值是≤180。

20. 根据权利要求18形成的酯产物混合物,其中所述还原布朗斯台德酸催化剂是膦酸(H_3PO_3)。

21. 一种制造聚酯的方法,该方法包括获得根据权利要求1或4所述的方法制造的异己糖醇酯单体,并且使所述异己糖醇酯单体单独地或与一种附加的单体聚合。

控制异己糖醇酯化中颜色体形成

[0001]　　优先权权益

[0002]　　本申请要求于2013年12月18日提交的美国临时申请号61/917,390以及2013年12月20日提交的美国临时申请号61/918,810的优先权的权益,这些申请的内容通过引用结合在此。

发明领域

[0003]　　本披露涉及作为聚合物合成中的单体、以及增塑剂、表面活性剂和中间体化学化合物有用的某些环状双官能材料。具体地,本发明涉及1,4:3,6-双脱水己糖醇的酯以及用于它们制备的方法。

[0004]　　背景

[0005]　　传统上,已经由石油衍生的原料制备了许多聚合物和商品化学品。随着石油供应变得越来越昂贵和难以获取,对于从生物衍生的源开发可再生的或"绿色的"替代材料用于将充当常规的、石油基或石油衍生的对应物的商业上可接受的替代品的化学品,或者用于生产与由化石(不可再生源)生产的相同的材料的兴趣和研究已经增加。

[0006]　　对于此类材料的生物衍生的或可再生的替代原料的最丰富种类之一是碳水化合物。然而,碳水化合物通常不适合现在的高温工业方法。与具有低官能度的石油基、疏水的脂肪族或芳香族的原料相比,碳水化合物(如糖)是复杂的、多官能化的亲水材料。其结果是,研究人员已经寻求生产以下生物基化学品,这些生物基化学品可以衍生自碳水化合物,但是它们是较小高度官能化的,包括更稳定的双官能化合物,如2,5-呋喃二甲酸(FDCA)、乙酰丙酸、以及1,4:3,6-双脱水己糖醇。

[0007]　　1,4:3,6-双脱水己糖醇(在此还被称为异己糖醇(isohexide))衍生自来自谷物基多糖的可再生资源。异己糖醇具体为一类衍生自相应的还原糖醇的二环呋喃二醇,例如取决于手性,对应地D-山梨糖醇、D-甘露糖醇、以及D-艾杜糖醇被脱水并且被环化成A)异山梨醇、B)异甘露糖醇、以及C)异艾杜糖醇,它们的结构在方案A中展示。

[0008]　　方案A:ABC

[0009]

来自D-山梨糖　　　来自D-甘露糖醇　　　来自D-艾杜糖
醇的异山梨醇　　　的异甘露糖醇　　　醇的异艾杜糖醇
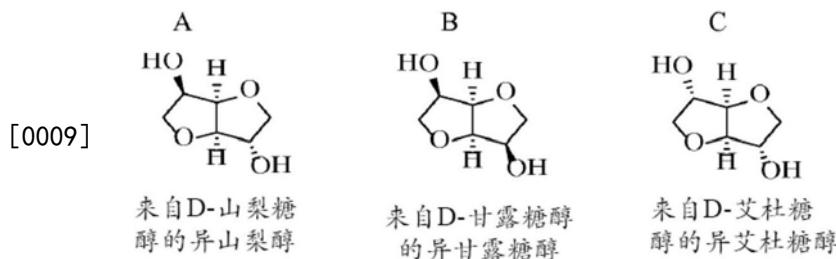
[0010]　　这些分子实体已经得到相当大的重视并且由于种种原因被认为是一种有价值的、有机化学支架。一些有益的属性包括它们的制备和纯化的相关便利性、所使用的母体原料的固有经济性,不仅由于它们的可再生的生物质来源(给予非常大的作为不可再生的石油化学产品的替代物的可能性),而且可能最显著地由于固有的手性双官能度,该双官能度允许设计并且合成几乎无限制扩张的衍生物。

[0011]　　这些异己糖醇由两个顺式稠合的四氢呋喃环构成,这些环是几乎平面的并且V形

3

的(具有在环之间120°角度)。这些羟基位于碳2和5处并且置于该V形分子的或者内部或者外部上。分别将它们指定为内型或外型。异艾杜糖醇具有两个外型羟基,而在异甘露糖醇中这些羟基都是内型,并且在异山梨醇中一个外型和一个内型羟基。这些外型取代基的存在增加了其所附接的环的稳定性。再者外型和内型基团展示了不同的反应性,因为它们取决于衍生反应的空间要求是更容易或更不容易接近的。

[0012] 随着在衍生自自然资源的化学品的兴趣的增加,潜在的工业应用已经在异己糖醇的生产和使用上产生兴趣。例如,在聚合物材料的领域中,这些工业应用包括使用这些二醇来合成或改性缩聚物。作为单体它们有吸引力的特征与它们的刚性、手性、无毒性、以及它们不是衍生自石油的事实相关。出于这些原因,具有优良的热机械耐受性和/或具有特定光学特性的高玻璃化转变温度聚合物的合成是可能的。再者这些分子的无害特征打开了在包装或医学设备中应用的可能性。例如,在大工业规模下以满足用于聚合物制造者的要求的纯度生产异山梨醇可能是用于作为一种工业聚合物应用的重要化合物出现的异山梨醇的基础。(参见例如,F.Fenouillot等人,"来自可再生的1,4:3,6-双脱水己糖醇(异山梨醇、异甘露糖醇以及异艾杜糖醇)的聚合物:综述(Polymers From Renewable1,4:3,6-Dianhydrohexitols(Isosorbide,Isommanide and Isoidide):A Review)"聚合物科学进展(Progress in Polymer Science),第35卷,第578-622页(2010);或者X.Feng等人,"环境可持续应用的糖基化学品(Sugar-based Chemicals for Environmentally sustainable Applications)"聚合物材料的现代科学(Contemporary Science of Polymeric Materials),美国化学会志(Am.Chem.Society),2010年12月;或者异山梨醇基增塑剂(isosorbide-based plasticizers),例如美国专利号6,395,810,各自的内容通过引用结合在此。)

[0013] 用使用异己糖醇来制造酯衍生物的常见缺点之一是这些合成反应产生作为衍生自使异己糖醇反应的一种副产物或者作为副产物化合物降解的颜色体的倾向。典型地,在升高的温度下、在氧存在下形成这些颜色体。鉴于酯显示了作为增塑剂、分散剂、润滑剂、调味剂、溶剂等的众多利用并且异己糖醇酯通常用作增塑剂和聚合物,并且其变体是积极地合成的并且被研究用于在相对于目前材料的这些领域中的增强的性能,合成具有较少颜色体的较大纯度的产物的更好的方法是令人希望的。一种减少颜色体的形成的方法将帮助制造商产生一种更好品质且更纯的最终产物。

[0014] 发明概述

[0015] 本披露部分地涉及一种用于从异己糖醇酯制备酯的方法。总体上,该方法涉及使一种异己糖醇和一种有机酸、在一种还原布朗斯台德酸催化剂存在下在最高达约250℃的温度下反应,持续一段足以产生该异己糖醇酯的时间,同时将一种产物混合物中的颜色体的形成限制为小于230的APHA值。该方法进一步包括在与该还原布朗斯台德酸反应之前在制备该异己糖醇或有机酸中减少现有者(incumbent)颜色体或颜色产生前体化合物。

[0016] 本发明纯化方法的另外的特征和优点将披露于以下详细说明中。应理解的是上述概述以及以下详细说明和实例都仅代表本发明,并且旨在提供理解如所要求的本发明的概述。

[0017] 附图简要说明

[0018] 图1描绘了根据本方法的实施例的异山梨醇酯的一种示例性合成。

[0019]　　图2示出了从通过根据本发明的实施例合成的异构体的气相色谱法(GC)进行的定量分析获得的结果的一幅色谱图。

[0020]　　图3是一幅曲线图,该曲线图示出了当在175℃下反应7小时时在膦酸(H₃PO₃)的百分比催化剂负载量与其对APHA值和异山梨醇的百分比转化率的影响之间的关系。

[0021]　　图4示出了与2-乙基-己酸(2EH)的原料溶液相比,在已经与H₃PO₃催化剂反应(175℃,7h)的异己糖醇酯产物混合物中的颜色衰减的对应程度的一系列照片。

[0022]　　图5示出了在对应地使用1wt.%和5wt.%的膦酸催化剂负载量从一种2EH的预蒸馏溶液(APHA 6)在205℃下7小时制备的异己糖醇产物混合物中的APHA颜色衰减的照片。

[0023]　　图6是对于约10g在空气中经受200℃持续1小时的异山梨醇产物混合物的高温热应力试验的结果的照片。

[0024]　　发明详细说明

[0025]　　第I部分-说明

[0026]　　作为提供非常大的作为不可再生的石油化学品的替代物的潜力的生物质衍生的化合物,1,4:3,6-双脱水己糖醇是一类作为可再生的分子实体有价值的二环呋喃二醇。(为了方便起见,1,4:3,6-双脱水己糖醇在以下说明中将被称为"异己糖醇")。如以上提到的,这些异己糖醇是优良的化学品平台,这些化学品平台由于它们固有的手性双官能度最近已经得到关注,该手性双官能度可以允许现存的和可合成的新的衍生化合物二者的显著发展。

[0027]　　异己糖醇起始材料可以通过对应地制造异山梨醇、异甘露糖醇、或异艾杜糖醇的已知的方法获得。异山梨醇和异甘露糖醇可以衍生自对应的糖醇(D-山梨糖醇和D甘露糖醇)的脱水。作为一种商业产品,异山梨醇还是容易从制造商可获得的。第三种异构体(异艾杜糖醇)可以从罕有地存在于自然中并且不能够从植物生物质中提取的1-艾杜糖产生。由于这个原因,研究人员已经积极地探索异艾杜糖醇的不同的合成方法。例如,异艾杜糖醇起始材料可以从异山梨醇通过差向异构作用制备。在L.W.Wright,J.D.Brandner,有机化学期刊(J.Org.Chem.),1964,29(10),第2979-2982页中,差向异构作用是借助于Ni催化剂使用负载在硅藻土上的镍诱导的。在相对苛刻的条件(如220℃至240℃的温度在150大气压的压力下)下进行该反应。在约两小时之后该反应达到稳态,其中平衡混合物包含异艾杜糖醇(57%-60%)、异山梨醇(30%-36%)和异甘露糖醇(5-7-8%)。当从异艾杜糖醇或异甘露糖醇开始时,获得了可比较的结果。增加pH至10-11发现具有促进的作用,与增加温度和镍催化剂浓度一样。在美国专利号3,023,223中可以发现类似的披露,其提出了将异山梨醇或异甘露糖醇异构化。最近,P.Fuertes提出了一种用于通过层析段分L-艾杜糖醇和L-山梨糖的混合物获得L-艾杜糖醇(异艾杜糖醇的前体)的方法(美国专利公开号2006/0096588;美国专利号7,674,381B2)。L-艾杜糖醇是从山梨糖醇开始制备的。在第一步骤中,将山梨糖醇通过发酵转化为L-山梨糖,随后将该L-山梨糖氢化为D-山梨糖醇和L-艾杜糖醇的混合物。然后将这种混合物转化为L-艾杜糖醇和L-山梨糖的混合物。在与L-山梨糖分离之后,可以将L-艾杜糖醇转化为异艾杜糖醇。因此,在四步反应中将山梨糖醇转化为异艾杜糖醇,产率为约50%。(参见,例如,国际专利申请WO13125950)所引用的参考文献的内容通过引用结合在此。

[0028]　　A.异己糖醇酯的制备

[0029]　　费歇尔-斯皮尔(Fischer-Speier)酯化是目前用于酯的工业制备的标准方案。费歇尔-斯皮尔酯化具体为一种使用布朗斯台德酸或路易斯酸催化剂用羧酸直接酰化醇的简单方法。然而，当在强酸催化剂存在下转化热敏底物如异己糖醇时，颜色是有问题的。希望是通过开发一种催化剂使下游加工单元操作最小化，该催化剂可以提供目标酯的相对高的产率(例如，≥55%-60%)同时使颜色体形成或增值最小化。

[0030]　　与典型地涉及至少两个操作步骤(该产物的合成反应接着纯化或脱色(例如，结晶、蒸馏和/或色谱法))的常规商业酯化方案相比，根据本发明的酯化方法是更简单的。该方法涉及一种单步操作。在该商业领域中，存在一种完全消除下游加工的希望。因此，在单反应中可以制造是无色亦或接近无色(所谓的"无色透明的")的产物或者是在可容许的颜色规格内的产物而无需另外的稍后纯化的一种方法就成本和效率而言将是相当有利的。

[0031]　　出于确定在该产物混合物中的颜色的可接受水平的目的，人们使用美国公共卫生协会命名的并且由ASTM D1209定义的APHA颜色标准，将其通过引用结合在此。(它最初旨在描述废水的颜色，但其使用已经扩充到包括其他工业应用。)APHA与色度色标试验类似，它使用一种铂-钴(Pt/Co)溶液，其中该水颜色可以用作所溶解的且微粒的材料的浓度的一种量度。杂质可以是深色的，例如溶解的有机化合物如单宁可以导致深棕色颜色。该APHA色标是从0至500，其中0是无色的并且500是最有色的。

[0032]　　本发明的一个特征是减少或消除可能在一种异己糖醇化合物的酯化过程中原位生成的颜色体的能力。这些颜色体或者被阻止形成或者使它们的量在所得产物混合物中最小化。该方法涉及：使一种异己糖醇和一种羧酸、在一种还原布朗斯台德酸催化剂存在下反应，持续一段足以产生展示小于230的APHA值的产物混合物的时间。典型地，该产物混合物展示了≤185的APHA值，令人希望地该APHA值是≤150。

[0033]　　该异己糖醇可以是：异山梨醇、异甘露糖醇、以及异艾杜糖醇中的至少一种。该有机酸可以是至少一种具有C_2-C_{26}的链烷酸、链烯酸、链炔酸和芳香族酸。该异己糖醇以至少40%的转化率被转化为一种相应的酯，令人希望地该转化率是约50%或更大。

[0034]　　在从约150℃或160℃至约240℃或250℃的范围内的温下进行该酯化。典型地，该反应温度是在从约170℃或175℃至约205℃或220℃的范围内。

[0035]　　该还原布朗斯台德酸催化剂以相对于异己糖醇的量的至少0.5wt.%的量存在。在某些实施例中，当该还原布朗斯台德酸催化剂的量是>5.0wt.%时，该产物混合物主要包含二酯。在其他实施例中，当该还原布朗斯台德酸催化剂以从约2.5wt.%至约5.0wt.%的量存在时，该产物混合物包含约1:1比率的单酯和二酯。在还其他实施例中，当该还原布朗斯台德酸催化剂量是以<2.5wt.%量存在时，该产物混合物主要包含单酯。

[0036]　　表1列出了就产物颜色、催化剂负载量，以及转化率而言相对于一种还原布朗斯台德酸作为对比实例的若干常规具有商业或潜在价值的酸催化剂物种。在此描述的这些方法通过使用作为该还原布朗斯台德酸的膦酸(H_3PO_3)(还被称为磷酸)进行例示。在表1中，这些对比实例倾向于产生具有超过250的APHA值的深色产物。

[0037]　　表1.催化剂、催化剂负载量，百分比(%)异山梨醇转化率、APHA颜色值

[0038]

催化剂	负载量（相对于异山梨醇是wt.%)	APHA	% 异山梨醇转化率
自动催化	0.0	500	23.39
Sn(II)2EH	9.9	500	66.23
Sn(II)2EH	5.1	500	42.11
(丁基)$_2$SnCl$_2$	5.2	500	38.66
HaCl$_4$	5.4	500	52.83
(丁基)$_2$Sn(月桂酸盐)$_2$	5.1	306	35.28
ZrCl$_4$	5.4	500	42.16
ZrCl$_4$	5.1	500	47.98
(丁基)$_2$Sn(马来酸盐)	5.3	319	38.48
SnCl$_4$	5.7	500	88.55
SnCl$_2$	5.7	277	87.99
BiCl$_3$	5.7	500	36.33
La(OTf)$_3$	1.0	500	82.49
二丁基锡(IV)氧化物	5.7	281	31.88
Fe(OTf)$_3$	1.0	500	69.91
预反应混合物		96	
膦酸	11.6	131	93.99
膦酸	6.7	145	83.73
膦酸	4.9	153	74.08
膦酸	3.6	168	58.79
膦酸	1.3	180	40.92
膦酸	0.6	196	28.43

[0039]　　　某些强的布朗斯台德酸或路易斯酸催化剂（例如，H_2SO_4)将产生颜色体。我们已经发现包含完成异山梨醇到该2-乙基己酸的对应的单和二酯的高转化率的一种还原布朗斯台德酸和一种或多种布朗斯台德和/或路易斯酸还可以伴随地减轻颜色体在产物中的积累。该酯化的产物混合物的颜色色泽随着该还原布朗斯台德酸催化剂的浓度的增加而降低。

[0040]　　　一种具体的还原布朗斯台德酸物种是膦酸(H_3PO_3)（还被称为磷酸），该膦酸是一种可商购的、廉价的结晶固体并且具有强酸度（pKa约1）。这种材料表明了在费歇尔酯化的背景下高催化活性以及该产物混合物的显著的颜色衰减两者。迄今为止，我们相信膦酸或者

作为异己糖醇与羧酸的酰化的催化中的一种布朗斯台德酸,关于产物的颜色减轻或者关于高的异己糖醇转化率,在此方面没有得到极大关注。此外,此时,膦酸是显示高反应性和伴随的颜色减少两者的物质。

[0041] 因此,出人意料发现的是,当以足够量(例如,≥1.0wt.%;优选地 ≥1.5wt.%或2.0wt.%)使用时尽管一种布朗斯台德酸(膦酸)不仅帮助催化并且增加由异己糖醇制造酯的转化率,而且还可以帮助显著减少产物混合物中的所不希望的颜色体的发展。根据一个具体的实施例,在异山梨醇到2-乙基己酸的单和二酯的酯化中,膦酸显示了高度有效的催化活性(约80%-95%)(即,与对于氯化锡展示的效能(约87%-89%)相似的效能)。

[0042] 膦酸证明是产生了到对应的单酯和二酯的高异山梨醇转化率,同时还显示了有效控制并且抑制产物混合物中的颜色体形成或累积的显著抗氧化剂特性。

[0043] 膦酸作为一种用于酰化反应的催化剂起作用,并且提供了一种帮助减轻颜色体形成的溶液中的强还原剂。尽管不受理论束缚,据信该膦酸可以与颜色体前体相互作用以阻止它们过渡到颜色实体。方案1说明了该反应的一个实施例。该反应简易地进行。

[0044] 方案1. 膦酸(H_3PO_3)催化异山梨醇到2-乙基己酸(2EH)的单酯和二酯的费歇尔酯化。

[0045]
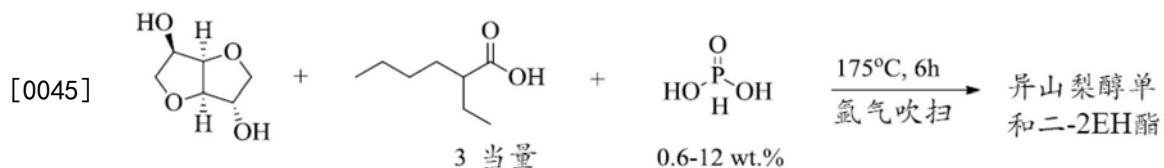
[0046] 根据本方法,该异己糖醇到其对应酯的转化率是约最小40%-50%。典型地,该异己糖醇转化率是约55%或更大、更典型地约65%或70%或更大(例如,约75%、80%、84%、87%、90%、92%、95%或更大)。

[0047] 虽然在此描述的方法用2-乙基己酸进行例示,但是该方法适合于与对于该异己糖醇酯化的所希望的任何有机酸一起使用,该有机酸包括C_2至C_{26}大小的链烷酸、链烯酸、以及芳香族酸,其条件仅是该有机酸可溶于反应混合物中。

[0048] 膦酸被报道为在200℃下分解为磷酸和膦,并且在此温度下又似乎不会不利地影响该酯化过程/颜色体减轻,如通过表2中的结果证明的,其中异山梨醇显示了完全转化为对应的酯(主要二酯),具有来自205℃下持续7h进行的反应的最小颜色增值。

[0049] 表2.用蒸馏过的2-乙基-己酸(2EH)、205℃、7h的H_3PO_3催化的异山梨醇酯化

[0050]

样品	比较	负载量（相对于异山梨醇的 wt.%）	APHA（颜色）	%异山梨醇转化率
1.	预反应混合物未蒸馏的 2EH		96	
2.	预反应混合物蒸馏过的 2EH		6	
3.	自动催化	0	263	5 h 下 57
4.	膦酸	1.20	136-138	5 h 下 85
5.	膦酸	5.48	98	5 h 下 100

[0051]　　作为使颜色最小化的方法的一部分,除了其他纯化技术之外人们可以或者在酯化之前预纯化这些起始试剂,例如通过蒸馏该链烷酸(还可以使用链烯酸或链炔酸),或者后续进行色谱法。与该自动催化值(APHA 263)相比,在该产物混合物中对应地使用以约1wt.%(APHA 136-138)和5wt.%(APHA 98)的浓度的膦酸的结果显示了相对良好的颜色衰减,并且在颜色上更加接近于澄清的蒸馏过的2EH溶液的颜色(APHA 6)。

[0052]　　膦酸的独特的特征是它不仅仅催化该反应,而且具有适合的还原剂潜能,并且因此可以进一步氧化为磷酸。在异己糖醇酯化的领域中,膦酸是迄今为止筛选过的看出高异山梨醇转化率和颜色减轻两者的那些中的唯一的催化剂。此外,没有区别用于此类行为(积极的催化、颜色减轻)的在前的文献。

[0053]　　其他人已使用一种水溶液次磷酸(H_3PO_2)。反应动力学可以与该次磷酸和膦酸的反应动力学类似,因为各自具有接近1的pKa。然而,对于这些酸的对比催化表明了这些酸各自展示的减轻颜色的化学过程很可能不同。次磷酸在130℃下降解,并且可以仅仅作为50%的水溶液获得,由于水的存在该次磷酸将不以与本反应系统中的膦酸类似的方式起作用。

[0054]　　作为示例性方法,用于异己糖醇(例如,异山梨醇)与羧酸(例如,2-乙基己酸)的酸催化的酯化的本合成方案涉及:在配备有锥形的、PTFE涂覆的磁力搅拌棒的三颈、500mL圆底烧瓶中装入50g异山梨醇(0.342mol)、148g的2-乙基己酸(1.026mol)和5wt.%酸催化剂(相对于异山梨醇)。该烧瓶的颈配备有迪安-斯达克分水器、氩气管线、以及由不锈钢热电偶在中心穿刺的橡胶隔片。将该烧瓶浸入在油浴中并且加热至175℃具有同时剧烈的氩气吹扫。每个小时取出等份部分并且通过气体色谱法进行分析。在7小时处停止该反应。图1说明了用于合成异山梨醇2EH单酯的本方法的实施例。

[0055]　　图2是从通过根据以上反应合成的四种异构体的两组气相色谱法(GC)进行的定量分析获得的结果的一幅代表性的色谱图。

[0056]　　三种因素(催化剂负载量、温度、和时间)的相互影响似乎促进该酯化反应的操作以产生低量的颜色体,这导致了一种更澄清的产物并且使一种用于下游纯化的需要最小化。违反直觉其中较大量的酸催化剂倾向于产生更多的颜色体的常规观察,使用膦酸的优点和意外结果之一是随着酸的催化剂负载量增加,颜色体的显示倾向于减小。图3是一幅曲

线图,该曲线图示出了当在175℃下反应7小时时在膦酸(H₃PO₃)的百分比催化剂负载量与其对APHA值和异山梨醇的百分比转化率的影响之间的关系。随着该酸催化剂浓度从1.3wt.%增加至11.6wt.%,产物混合物的APHA颜色值从181减少至137,并且转化率从约45%增加至约94%。

[0057]　　图4示出了根据本方法的经受酰化的异山梨醇产物的若干照片。这些所附照片突出显示出膦酸的双重作用催化和氧清除作用。与具有96的APHA色调计值的原料2-乙基己酸A相比,用以对应地1wt.%B、2.5wt.%C、5wt.%D、和10wt.%E催化剂负载量的膦酸反应(175℃下持续7h)的产物混合物样品示出了减少的颜色(对应地192、175、145、和137的APHA值),同时异山梨醇的转化产率对应地从43.56%、55.22%、86.52%增加至99.39%。换言之,用较大量的催化剂,人们可以实现较大的产率或异己糖醇的转化率同时仍然维持一种具有小于约200的APHA值的具有良好颜色品质的澄清溶液。对于这种现象的试验结果汇总于表1和3中,它们对应地在205℃和175℃下反应持续7小时。

[0058]　　表3.H₃PO₃催化结果:2-乙基-己酸与异山梨醇175℃、7h的酯化

[0059]

样品	负载量(相对于异山梨醇的 wt.%)	APHA (颜色)	%异山梨醇转化率	外型/内型(平均)	外型/内型(标准偏差)	%CV
1. 对比	0	96				
2.	11.6	137	93.99	4.05	0.07	1.59
3.	6.7	145	87.73	3.95	0.08	2.02
4.	4.9	151	85.92	4.09	0.08	2.02
5.	3.6	168	58.79	4.02	0.10	2.37
6.	1.3	181	44.92	3.96	0.08	2.00

[0060]　　注意:来自典型使用的催化剂的样品的产物混合物显示APHA>275。

[0061]　　附加地,如表3中的结果,表明了膦酸展示了以约4:1比率的异己糖醇分子的外型-OH比内型OH的更大的区域选择性。

[0062]　　图5是照片,这些照片示出与一种2EH的预蒸馏溶液(APHA 6)相比,与在205℃下7小时对应地在1wt.%和5wt.%的膦酸催化剂负载量增加有关的异己糖醇产物混合物中的APHA颜色值(APHA 136,98)的减少。

[0063]　　图6示出了探索对于减轻颜色该酸催化剂的氧清除潜力的高温热应力试验的结果的照片。该试验样品包含约10g异山梨醇产物混合物,将该产物混合物在空气中经受200℃持续1小时。这些结果说明了就添加至该异山梨醇混合物中的膦酸的量而言良好的氧清除性能和/或使从异山梨醇的热氧化分解产生的颜色体前体不适用的能力的一个窗口。一种不包含膦酸的异山梨醇产物样品展示了很浅清澄的颜色(APHA约76),而在约90,000ppm(900mg)的量的膦酸下,该溶液展示了深暗色(APHA 500)。对应地在约100ppm、300ppm、1000ppm的膦酸负载量下,该溶液的颜色随着增加的浓度而减轻(对应地,APHA>500、278、191、158)。然而,在约40,000ppm(400mg)的浓度下,该溶液的颜色再次变暗(APHA 465)。这

表明了该窗口具有用于在维持将颜色体发展控制到相对低水平下(在约76与约105之间的APHA值下)是有效的在约2,000ppm(0.2wt.%)(APHA98)至约5,000ppm(0.5wt.%)或约10,000ppm(1.0wt.%)之间的膦酸量的下限和上限。

[0064]　　表4,异己糖醇与2-乙基-己酸的膦酸催化剂的酯化

[0065]

异己糖醇	催化剂负载量(相对于异己糖醇的 wt.%)	APHA(未稀释地,色调计)	百分比(%)异己糖醇转化率	
异山梨醇	4.9	151	85.92	
异甘露糖醇	5.3	210	75.27	
异艾杜糖醇*	5.2	187	99.69	

[0066]　　*约80%纯度,THF饱和的

[0067]　　关于在表4中呈现的三种具体的异己糖醇,当使用膦酸催化剂反应时,相对于或者异艾杜糖醇(APHA187)或异甘露糖醇(APHA 210),异山梨醇(APHA 151)示出了最好的性能与更好的颜色衰减。这可能是异甘露糖醇和异艾杜糖醇的性质的一种结果。异甘露糖醇比异山梨醇更加的热氧化地不稳定。尽管如此,对于异甘露糖醇的210的APHA值是比典型的远远更低的颜色产生。通常,当用常规催化剂酯化异甘露糖醇时,该产物将显示大大超过500的APHA颜色值。在另一个实例中,异甘露糖醇与7.6wt.%膦酸(相对于异甘露糖醇)在175℃下在7小时内反应并且产生89.44%的异甘露糖醇转化率(APHA 210)。在该表中示出的具体的异艾杜糖醇样品是约80%纯的,包含显著量的THF,该样品是一种容易易受热氧化分解影响的物种,并且因此产生颜色体。我们相信对于一种更大纯度(例如,接近100%纯度)的异艾杜糖醇样品,人们将看见比指出的颜色更大的颜色减少。该异艾杜糖醇产物将具有与该异山梨醇样品的着色可比较的或比其更好的着色。

[0068]　　聚酯可以从根据本方法制备的具有≤150的APHA值的异己糖醇酯(例如,异山梨醇酯)制造。因此,人们可以使用一种通过以下方式制造聚酯的方法,获得一种根据在此描述的这些方法制造的异己糖醇酯单体,并且使所述异己糖醇酯单体单独地或与一种附加的单体聚合。

[0069]　　已总体地并借助于实例详细地描述了本发明。本领域的普通技术人员应理解,本发明不必然限于特定披露的实施例,而是在不脱离如由以下权利要求书或其等效物(包括目前已知或有待开发的其他等效组分,它们可以在本发明的范围内使用)所定义的本发明的范围的情况下可以作出修改和变化。因此,除非变化另外脱离本发明的范围,否则这些变化应被解释为被包括在此。

图1

图2

图3

图4

图5

图6