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Low temperature, single solvent process for the production of sucrose-6-ester

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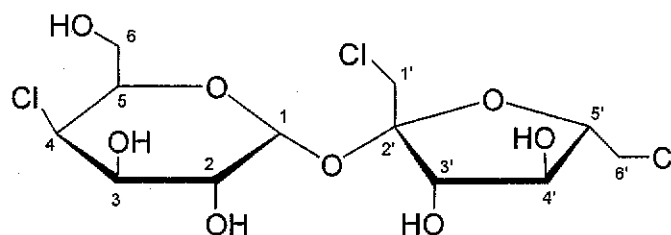
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TITLE**LOW TEMPERATURE, SINGLE SOLVENT PROCESS FOR THE PRODUCTION OF SUCROSE-6-ESTER****FIELD OF THE INVENTION**

5 This invention relates to sucrose-6-esters and to methods for their preparation. In particular, this invention relates to methods for the preparation of sucrose-6-esters in which water of reaction is removed at a temperature that does not exceed 78°C.

BACKGROUND OF THE INVENTION

10 Sucralose (4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose), a high-intensity sweetener that can be used in many food and beverage applications, is a galacto-sucrose having the following molecular structure:

**SUCRALOSE**

15 Sucralose is made from sucrose by converting the hydroxyls in the 4, 1' and 6' positions to chloro groups. In this process, the stereochemical configuration at the 4 position is inverted.

20 In one process for making sucralose from sucrose, sucrose is first converted to a sucrose-6-ester, such as sucrose-6-acetate or sucrose-6-benzoate. The sucrose-6-ester is chlorinated by reaction with a chlorination agent and a tertiary amide, and the resulting reaction mixture heated and then quenched with aqueous alkali. The resulting 4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose ester (sucralose-6-ester) is converted to sucralose, which is subsequently purified and isolated.

25 Sankey, U.S. Patent 5,470,969; Vernon, EP 0 475 619; Clark, U.S. Patent 6,939,962; and White, EP 0 776 903, the disclosures of which are all incorporated herein by reference, disclose processes for the synthesis of a sucrose-6-ester. The process disclosed by Clark comprises: (a) reacting sucrose in a polar aprotic solvent, such as *N,N*-dimethyl formamide,

with an organotin-based acylation promoter, while continuously adding a non-polar co-solvent capable of removing water by co-distillation, and removing water by co-distillation, to afford a reaction mixture which is substantially free from water, followed by (b) adding a carboxylic anhydride to the reaction mixture and maintaining the resulting reaction mixture at a temperature and for a period of time sufficient to produce a sucrose-6-ester. The non-polar co-solvent is typically a hydrocarbon, such as cyclohexane, *n*-heptane, toluene, or isooctane.

This process requires large amounts of the non-polar co-solvent, which must be dried before addition and then recovered and re-dried for reuse. Step (a) operates in a temperature region in which decomposition of carbohydrates may occur – even with relatively short reaction times of 20-30 minutes. Because the non-polar co-solvent can cause precipitation of sucrose, the maximum sucrose concentration that can be used in the process is limited by the presence of the non-polar co-solvent. In addition, unreacted sucrose remaining in the sucrose-6-ester product can produce undesirable and difficult to remove tetra-chlorinated species in the subsequent chlorination step. Therefore, a need exists for a process for forming a sucrose-6-ester from sucrose that does not have these disadvantages.

Micinski, PCT Patent Application Publication No. WO2008/084197, discloses a process for the synthesis of a sucrose-6-ester comprising: (a) forming a first reaction mixture comprising sucrose, a polar aprotic solvent, such as *N,N*-dimethyl formamide, and an organotin-based acylation promoter; (b) removal of water from said first reaction mixture by contacting, in a continuous counter-current manner, with gas or solvent vapour capable of removing water at a temperature, pressure and residence time sufficient to afford a second reaction mixture which is substantially free from water; followed by (c) adding a carboxylic anhydride to said second reaction mixture to afford a third reaction mixture, and maintaining said third reaction mixture at a temperature and for a period of time sufficient to produce a sucrose-6-ester.

This process requires the use of a gas or solvent vapour capable of removing water. According to the present invention, it has been unexpectedly found that use of a gas or solvent vapour capable of removing water is not necessary, and a simpler process has been achieved.

SUMMARY OF THE INVENTION

The invention is a process for producing a sucrose-6-ester. In one aspect the invention is a process comprising, in order, the steps of:

(a) providing a first reaction mixture comprising sucrose, a polar aprotic solvent and an organotin-based acylation promoter;

(b) removing water formed by reaction of sucrose with the organotin-based acylation promoter from the first reaction mixture to afford a second reaction mixture that is substantially free from water, and

(c) adding a carboxylic acid anhydride to the second reaction mixture to afford a third reaction mixture, thereby producing a sucrose-6-ester;

in which:

a non-polar co-solvent is not added during step (b); and

in step (b), the temperature does not exceed 78°C.

In one aspect of the invention, during step (b), water is removed by distilling the water with the polar aprotic solvent at reduced pressure. In one aspect of the invention, in steps (a) and (b), the first reaction mixture and/or the second reaction mixture consist essentially of sucrose, the polar aprotic solvent, the organotin-based acylation promoter, and/or their reaction products. In one aspect of the invention, the organotin-based acylation promoter is 1,3-diacetoxy-1,1,3,3-tetrabutyl-distannoxane (distannoxane diacetate or DSDA). In one aspect of the invention, the polar aprotic solvent is *N,N*-dimethyl formamide. In one aspect of the invention, the carboxylic acid anhydride is acetic anhydride and the sucrose-6-ester is sucrose-6-acetate. In one aspect of the invention, step (c) is carried out at less than 10°C.

In step (b), the water formed by reaction of sucrose with the organotin-based acylation promoter is quickly and efficiently removed. Because the water of reaction is removed at a lower temperature than in previous processes, the amount of carbohydrate decomposition is drastically reduced, even when extended reaction times are used. However, because the reaction proceeds efficiently, even at reduced temperatures, extended reaction times are not necessary.

Because a non-polar solvent is not necessary to remove water, addition of the non-polar co-solvent to remove water is completely eliminated. This simplifies the process because it is not necessary to recover and dry large amounts of non-polar co-solvent for reuse. Because the process operates at higher concentrations and uses different methods for water removal than previous processes, less energy is used to heat the reaction mixture,

which produces a saving in energy cost. In addition, at lower temperatures the reaction has higher selectivity with almost no decomposition, which increases the overall yield of the

sucralose preparation process. The process is also more economical to operate because higher concentrations of sucrose can be used, the possibility of sucrose precipitation during the process is reduced, and smaller and consequently less expensive equipment can be used to carry out the process.

5 Furthermore, use of a gas or solvent vapour capable of removing water is not necessary, resulting in a simpler process. Thus, according to the present invention, the mixture in step (b) is preferably not contacted with a gas or solvent vapour capable of removing water. In particular, the mixture in step (b) is preferably not contacted in a continuous counter-current manner with a gas or solvent vapour capable of removing water.

10 BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a flow diagram showing a low temperature, single solvent process for the production of sucrose-6-ester.

DETAILED DESCRIPTION OF THE INVENTION

15 Unless the context indicates otherwise, in the specification and claims, the terms organotin-based acylation promoter, polar aprotic solvent, carboxylic acid anhydride, non-polar co-solvent, and similar terms also include mixtures of such materials. Unless otherwise specified, all percentages are percentages by weight and all temperatures are in degrees Centigrade (degrees Celsius). Reduced pressure refers to a pressure less than atmospheric pressure. Temperature refers to the temperature of the relevant reaction
20 mixture, that is, the internal temperature of the liquid phase. (For the avoidance of doubt, it does not refer to the temperature of a heat source, which will, in general, be higher than the internal temperature of the reaction mixture being heated, or of a cooling source, which will, in general, be lower than the internal temperature of the reaction mixture being cooled). Reduced temperature refers to a temperature that is less than the boiling point of
25 the particular polar aprotic solvent present in the reaction mixture at atmospheric pressure.

A process for the preparation of sucralose from sucrose involves the following steps. First, the reactive hydroxyl in the 6-position of sucrose is blocked with an ester group, such as acetate or benzoate. The hydroxyls in the 4, 1' and 6'-positions of the resulting sucrose 6-ester are converted to chloro groups, with inversion of the stereochemical configuration at
30 the 4-position. Then the ester group in the 6-position of the resulting sucralose-6-ester is removed, and sucralose, the resulting product, purified and isolated. The process, or individual steps thereof, can be either batch or continuous processes.

Preparation of Sucrose-6-Ester

Selective protection of the 6-hydroxyl of sucrose can be carried out by reaction of sucrose with a carboxylic acid anhydride, such as acetic anhydride or benzoic anhydride, in an anhydrous polar aprotic solvent in the presence of an organotin-based acylation promoter, under the reaction conditions described herein, at a temperature and for a period of time sufficient to produce the sucrose-6-ester. The 6-ester group shields the hydroxyl on the 6 position from the chlorination reaction. Accordingly, any ester group that is stable to the conditions of the chlorination reaction and which can be removed under conditions that do not affect the resulting sucralose can be used. When sucrose-6-acetate is prepared, 1,3-diacetoxy-1,1,3,3-tetrabutyl-distannoxane, for example, can be used as the organotin-based acylation promoter and acetic anhydride as the carboxylic acid anhydride. Preparation of sucrose-6-esters is disclosed in, for example, O'Brien, U.S. Pat. No. 4,783,526; Navia, U.S. Pat. No. 4,950,746; Simpson, U.S. Pat. No. 4,889,928; Neiditch, U.S. Pat. No. 5,023,329; Walkup, U.S. Pat. No. 5,089,608; Vernon, U.S. Pat. No. 5,034,551; Sankey, U.S. Pat. No. 5,470,969; Kahn, U.S. Pat. No. 5,440,026; Clark, U.S. Pat. No. 6,939,962, and Li, U.S. Pat. Pub. 2007/0227897 A1; the disclosures of which are all incorporated herein by reference.

A typical preparation of sucrose-6-ester employs a two-step process. First, sucrose is contacted in a solvent with an organotin-based acylation promoter and water of reaction is removed to form a tin-sucrose adduct. Then, the reaction mixture containing the tin-sucrose adduct is contacted with a carboxylic acid anhydride. The sucrose-6-ester can be isolated from the resulting reaction mixture. Alternatively, the organotin acylation promoter and/or its reaction products can be removed from the reaction mixture, and the resulting solution of the sucrose-6-ester in the polar aprotic solvent used in the next step, conversion of the hydroxyls at the 4, 1', and 6'-positions to chloro groups.

The choice of polar aprotic solvent is determined by the solubility in the solvent of sucrose, the organotin-based acylation promoter, and the resulting stannylated sucrose product, as well as by safety and toxicity considerations. Preferably the boiling point of the polar aprotic solvent is greater than the boiling point of water at atmospheric pressure. More preferably the boiling point of the polar aprotic solvent is at least 50°C greater than the boiling point of water at atmospheric pressure. Suitable polar aprotic solvents are, for example, *N*-methyl-2-pyrrolidone, dimethyl sulfoxide, *N,N*-dimethyl acetamide, hexamethylphosphoramide, *N,N*-diethyl formamide, *N,N*-diethyl acetamide and, preferably, *N,N*-dimethyl formamide.

The amount of the polar aprotic solvent to be used will also be determined chiefly by the above-mentioned solubility considerations. In general terms, it should be noted that the amount of polar aprotic solvent required according to the present invention can typically be less than for prior art systems in which a non-polar co-solvent is added. This is because the solubility of the reaction components in the solvent system is reduced by the presence of a non-polar co-solvent, so that a greater amount of polar aprotic solvent is then required to retain the reaction components in solution. Accordingly, when no non-polar co-solvent is present in accordance with the present invention, less polar aprotic solvent needs to be used. This provides advantages in terms of the downstream processing of the reaction mixture, as well as economic and environmental advantages. When the polar aprotic solvent is *N,N*-dimethyl formamide, typically about 4 g to about 22 g of polar aprotic solvent per 1 g of sucrose, preferably about 7 g to about 16 g of polar aprotic solvent per 1 g of sucrose, can be used.

The organotin-based acylation promoter can be any of those known in the art, for example, any of those disclosed in Navia, U.S. Pat. No. 4,950,746; Neiditch, U.S. Pat. No. 5,023,329; Walkup, U.S. Pat. No. 5,089,608; and/or Vernon, EP-0 475 619-A, the disclosures of which are all incorporated herein by reference. In particular, the organotin-based acylation promoter can be: a 1,3-di(hydrocarbyloxy)-1,1,3,3-tetra(hydrocarbyl)distannoxane; a di(hydrocarbyl)tin oxide; the reaction product of a di(hydrocarbyl)tin oxide and a dihydric alcohol, an alkanolamine, or an enolizable α -hydroxyketone; and a 1,3-diacyloxy-1,1,3,3-tetra-(hydrocarbyl)distannoxane. The term "hydrocarbyl" refers to an alkyl, cycloalkyl, aryl, or aralkyl group. The organotin-based acylation promoter is preferably a 1,3-diacyloxy-1,1,3,3-tetra-(hydrocarbyl)distannoxane.

When the organotin-based acylation promoter is a 1,3-di(hydrocarbyloxy)-1,1,3,3-tetra-(hydrocarbyl)distannoxane, the hydrocarbyloxy group is preferably a C_1 - C_8 alkoxy group or phenoxy, more preferably methoxy, ethoxy, *n*-propyloxy, *n*-butyloxy, *n*-pentyloxy or *n*-hexyloxy, and most preferably a methoxy group. The hydrocarbyl group in turn is preferably an alkyl group, more preferably a C_1 - C_8 alkyl group, and most preferably an *n*-butyl group.

When the organotin-based acylation promoter is a di(hydrocarbyl)tin oxide, the hydrocarbyl group is preferably an alkyl group, more preferably a C_1 - C_8 alkyl group, and most preferably an *n*-butyl group.

When the organotin-based acylation promoter is the reaction product of a di(hydrocarbyl)tin oxide and a dihydric alcohol, an alkanolamine, or an enolizable α -

hydroxyketone, the di(hydrocarbyl)tin oxide is preferably as described above. The dihydric alcohol can be an alkane diol, preferably having from 2 to 8 carbon atoms. Suitable examples are ethylene glycol, 2,3-propanediol, 2,3-butanediol, 1,3-butanediol, 1,4-butanediol, 1,3-propanediol, 1,2-pentanediol, and 1,2-hexanediol. Alternatively, the dihydric alcohol can be a cycloalkane diol, preferably having from 5 to 8 carbon atoms. Suitable examples are 1,2-cyclohexanediol and 1,2-cyclopentanediol. In each case, the two hydroxyl groups are preferably not more than four carbon atoms distant from each other on the carbon chain to which they are bonded, and preferably they are on adjacent carbon atoms or there is one carbon atom separating the carbon atoms to which the hydroxyl groups are bonded. The alkanolamine is preferably a C₂-C₈ alkanolamine, and preferably the hydroxyl group and the amino group are not more than four carbon atoms distant from each other on the carbon chain to which they are bonded, and more preferably the hydroxyl group and the amino group are on adjacent carbon atoms or there is only one carbon atom separating the carbon atoms to which the hydroxyl group and the amino group are bonded. Suitable alkanolamines are ethanolamine, 2-amino-1-propanol, and 1-amino-2-propanol. Suitable enolizable α -hydroxyketones are 2-hydroxy-2-phenylacetophenone and 3-hydroxy-2-butanone.

In some embodiments, the organotin-based acylation promoter is a 1,3-diacyloxy-1,1,3,3-tetra-(hydrocarbyl)distannoxane. The hydrocarbyl group of the 1,3-diacyloxy-1,1,3,3-tetra-(hydrocarbyl)distannoxane is preferably an alkyl group, more preferably a C₁-C₈ alkyl group, and most preferably a butyl group, so that 1,1,3,3-tetrabutyl-distannoxanes are particularly preferred. It is convenient if the acyloxy group matches that of the carboxylic anhydride to be used, so that, for example, when a sucrose-6-acetate is being prepared, 1,3-diacetoxy-1,1,3,3-tetrabutyl-distannoxane (distannoxane diacetate or DSDA) is most preferred.

When the organotin-based acylation promoter is a dinuclear species containing two atoms of tin per molecule (e.g. a distannoxane), preferably 0.5 to 2.5 molar equivalents, more preferably 0.75 to 1.2 molar equivalents, still more preferably 0.9 to 1.1 molar equivalents, and most preferably 1.0 molar equivalents of acylation promoter per mole of sucrose is present in the reaction mixture. When the organotin-based acylation promoter is a mononuclear species containing one atom of tin per molecule (e.g. a di(hydrocarbyl)tin oxide), preferably 0.5 to 2.5 molar equivalents, more preferably 0.8 to 1.5 molar equivalents, and most preferably 1.2 molar equivalents of acylation promoter per mole of sucrose is present in the reaction mixture.

In the first step (step (a)), a first reaction mixture comprising sucrose in a polar aprotic solvent is prepared by dissolving sucrose in the polar aprotic solvent, typically *N,N*-dimethyl formamide. Slight heating can be used to dissolve the sucrose. Then the organotin-based acylation promoter is added to the reaction mixture. Then, in step (b), in one aspect of the invention, the water and at least a portion of the polar aprotic solvent is removed from the first reaction mixture by distillation at reduced pressure. The polar aprotic solvent vapor removes the water of reaction and drives the reaction to the sucrose tin adduct in a very efficient manner, thereby affording the second reaction mixture.

An added non-polar co-solvent capable of removing water by co-distillation, such as described in Sankey, U.S. Pat. No. 5,470,969; White, EP 0 776 903; and Vernon, EP 0 475 619, the disclosures of which are incorporated herein by reference, is not necessary for efficient removal of the water of reaction. Consequently, in the current invention, the reaction is carried out without addition of such a non-polar co-solvent. Such solvents are typically ones that do not react with the polar aprotic solvent, the organotin-based acylation promoter, or the sucrose; that produce a mixture with the polar aprotic solvent, the organotin-based acylation promoter, and the sucrose; that reflux with an internal reaction temperature within the range of from about 75°C to about 153°C, preferably less than 100°C; that co-distill with water; and that do not render the sucrose insoluble. Such solvents are typically those that are immiscible with water and form a constant-composition minimum-boiling azeotrope with water, such as saturated hydrocarbons, aromatic hydrocarbons, chlorinated hydrocarbons, ketones, and ethers. Examples of such solvents include cyclohexane, *n*-heptane, toluene, and isooctane (2,2,4-trimethylpentane). In one further aspect of the invention, the first reaction mixture, and the second reaction mixture, formed after removal of water and at least a portion of the polar aprotic solvent by distillation under reduced pressure, consist essentially of the sucrose, the polar aprotic solvent, the organotin-based acylation promoter, and their reaction products.

In the distillation process of this embodiment of step (b), unlike in the process of Micinski, PCT Patent Application Publication no. WO2008/084197, a gas or solvent vapour capable of removing water is preferably not employed, other than the polar aprotic solvent itself. Thus, the mixture in step (b) is preferably not contacted with a gas or solvent vapour capable of removing water, other than the polar aprotic solvent itself. Examples of the gas used in the process of Micinski are nitrogen, argon, air, helium, and carbon dioxide. Examples of the classes of solvent vapour used in the process of Micinski are saturated hydrocarbons, aromatic hydrocarbons, chlorinated hydrocarbons, ketones, esters, and

ethers. Specific examples of the solvent vapour are cyclohexane, *n*-heptane, isooctane (2,2,4-trimethylpentane), benzene, toluene, diethyl ether, chloroform, carbon tetrachloride, hexane, ethyl acetate, and methyl acetate. Hydrocarbons are preferred, and cyclohexane, *n*-heptane, toluene, and isooctane (2,2,4-trimethylpentane) are particularly preferred.

5 In step (b), the removal of water and at least a portion of the polar aprotic solvent, the polar aprotic solvent is removed under reduced pressure, that is, a pressure less than atmospheric pressure. A reduced temperature, that is a temperature less than the boiling point of the polar aprotic solvent at atmospheric pressure, is also used. The temperature of the reaction mixture does not exceed 78°C. Preferably the temperature of the first reaction
10 mixture does not exceed about 75°C, or about 70°C during removal of the polar aprotic solvent. In other embodiments, the temperature of the reaction mixture in the first step is below 60°C or below 50°C during removal of the polar aprotic solvent. Preferably, the temperature of the first reaction mixture is maintained between about 78°C and about 5°C, between about 75°C and about 10°C, or between about 70°C and about 15°C, during the
15 removal of the polar aprotic solvent.

The temperature can be controlled by controlling the pressure at which the polar aprotic solvent is removed. Preferably the pressure is between about 65 mmHg (about 8.7 kPa) and about 0.5 mmHg (about 0.1 kPa), between about 50 mmHg (about 6.7 kPa) and about 15 mmHg (about 2.0 kPa), or between about 40 mmHg (about 5.3 kPa) and
20 about 20 mmHg (about 2.7 kPa) during removal of the polar aprotic solvent.

By use of this method, removal of the water of reaction can be achieved at a significantly lower temperature than previous methods. The lower temperature causes significantly less carbohydrate decomposition, even with extended reaction times. However, because the reaction proceeds efficiently, even at reduced temperatures, extended reaction
25 times are not necessary. Removal of the water of reaction is also accomplished without an added non-polar co-solvent. The resulting product stream is a clear, very slightly yellow product, compared with the darker material produced by other processes.

As will be apparent to those skilled in the art, the organotin-based acylation promoter can be introduced into the reaction mixture by addition of a solution of the
30 organotin-based acylation promoter in a non-polar aprotic solvent, such as one of the non-polar co-solvents capable of removing water by co-distillation discussed above. For example, the organotin-based acylation promoter can be added to the reaction mixture in cyclohexane solution. Consequently, a small amount (for example less than 30% w/w, less than 20% w/w, less than 15% w/w, or less than 10% w/w with respect to the reaction

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After sufficient time at a temperature near or below room (*i.e.*, ambient) temperature, the mixture is quenched with water. The course of the reaction can be followed by, for example, high pressure liquid chromatography.

The organotin-based acylation promoter is available for recycle after separation for the sucrose-6-ester. A process for the recovery and re-use of the organotin-based acylation promoter is disclosed in Vernon, U.S. Patent 5,034,551, the disclosure of which is incorporated herein by reference. When the organotin-based acylation promoter is a 1,3-diacyloxy-1,1,3,3-tetra-(hydrocarbyl)distannoxane, it is preferably recovered after step (c) and reused. A small amount of water and, if necessary, a small amount of a non-polar aprotic solvent, typically a hydrocarbon such as cyclohexane, are added to the reaction mixture after step (c). The reaction mixture partitions between water and the non-polar aprotic solvent, creating an upper (*i.e.*, less dense) phase comprising 1,3-diacyloxy-1,1,3,3-tetra-(hydrocarbyl)distannoxane and the non-polar aprotic solvent, and a lower (*i.e.*, more dense) phase comprising the sucrose-6-ester; the polar aprotic solvent, for example, *N,N*-dimethyl formamide; water; and carboxylic acid. The upper phase is removed, and the lower phase extracted with the non-polar aprotic solvent. The non-polar aprotic solvent extracts are combined and concentrated, preferably under reduced pressure, and treated with an alkoxide. The recovered 1,3-diacyloxy-1,1,3,3-tetra-(hydrocarbyl)distannoxane can be further purified by conventional techniques.

The lower layer contains sucrose-6-ester, carboxylic acid (that was formed by the reaction of carboxylic acid anhydride and sucrose plus any that might have been formed by hydrolysis of excess anhydride with the added water), unreacted sucrose, a small amount of other sucrose esters, and the polar aprotic solvent. Preferably, the carboxylic acid is removed from the solution of sucrose-6-ester in polar aprotic solvent prior to further processing of the sucrose-6-ester. When the acid is relatively volatile such as acetic acid, it can be removed, for example, by fractional distillation under reduced pressure, to remove water, any remaining non-polar aprotic solvent, and carboxylic acid. Make-up polar aprotic solvent can be added during or after the distillation, especially if the resulting mixture containing the sucrose-6-ester is to be further processed in the same solvent, such as in *N,N*-dimethyl formamide. The sucrose-6-ester in residual polar aprotic solvent may then be used directly in, for example, the chlorination process disclosed in Walkup, U.S. Patent 4,980,463, the disclosure of which is incorporated herein by reference. Optionally, sucrose-6-ester can be recovered by conventional procedures such as crystallization from a solvent such as methanol and used in the chlorination process.

The sucrose-6-ester is obtained with high selectivity and in high yield. When the sucrose-6-ester is sucrose-6-acetate, the selectivity of the 6-monoacetate over other acetylated products is very high, with normalized assays of 6-monoacetate as high as 85-90% relative to total carbohydrates. Unreacted sucrose, which produces undesirable and difficult to remove tetra-chlorinated species in the chlorination step, can be reduced to <0.1%.

This process can be run as a simple batch process. Alternatively, the process can be carried out as batch process in which the polar aprotic solvent is continuously added and removed, followed by a period in which the polar aprotic solvent is removed but no additional polar aprotic solvent is added.

Alternatively, the process of the invention can be carried out as a continuous process.

One embodiment of a process according to the present invention is shown in Figure 1. Referring to Figure 1, a solution containing sucrose (typically about 8-10%) in a polar aprotic solvent, such as *N,N*-dimethyl formamide, is added to a vessel (10). An organotin-based acylation promoter, such as 1,3-diacetoxy-1,1,3,3-tetrabutyl-distannoxane (DSDA) is also added.

A vacuum is maintained by a vacuum pump (12). The vapors of the polar aprotic solvent are condensed by a condenser (14).

The pressure in vessel (10) is selected so that the temperature of the reaction mixture does not exceed 78°C. As will be apparent to those skilled in the art, the temperature of the reaction mixture can be adjusted to temperatures not exceeding 78°C by reducing the pressure in vessel (10). Heat can be added to the vessel (10) via an external heat exchanger (16). Alternatively or additionally, heat may be added to vessel (10) by a heating jacket (not shown in the Figure) on the vessel (10).

A stream from the bottom of vessel (10) is taken into a reactor where it is cooled and acylated as previously described. The stream can be fed into the acylation reactor by any convenient means, for example by a circulation pump (18).

In an alternative embodiment not illustrated, dry vapors of the polar aprotic solvent can be generated separately and fed to vessel (10). This would permit a more concentrated solution of sucrose in the polar aprotic solvent to be fed to vessel (10). A more concentrated solution would decrease the liquid loading in vessel (10) while increasing the average residence time.

It is important that the feed to the acylation reaction be extremely dry. If desired, an additional water removal process (not shown) can be used prior to acylation. For example, a small single stage flash unit can be inserted between the vessel (10) and the acylation reactor to remove any small amount of water that may have been introduced into the process.

Conversion of Sucrose-6-Ester to Sucralose-6-Ester

To convert sucrose-6-ester to sucralose-6-ester, the hydroxyls at the 4, 1', and 6' positions of sucrose-6-ester are converted to chloro groups and the stereochemical configuration at the 4 position is inverted. Conversion of the hydroxyls in the 4, 1', and 6' positions of the ester to chloro groups with inversion of the stereochemical configuration at the 4 position is disclosed in Walkup, U.S. Pat. No. 4,980,463; Jai, U.S. Pat. Pub. 2006/0205936 A1; and Fry, U.S. Pat. Pub. 2007/0100139 A1; the disclosures of which are all incorporated herein by reference.

This chlorination process comprises the following steps. A reaction mixture is prepared comprising the sucrose-6-ester, a tertiary amide, and at least seven molar equivalents of a chlorination agent. For example, in one process, the sucrose-6-ester can be added in a feed stream that comprises about 20 wt% to about 40 wt% of the sucrose-6-ester. The ratio by weight of tertiary amide to total carbohydrate in the reaction mixture may be about 5:1 to about 12:1. Alternatively, a preformed chloroformiminium salt, such as (chloromethylene)dimethylammonium chloride (Arnold's reagent), can be used. (Chloromethylene)dimethylammonium chloride can be prepared, for example, by the reaction of phosgene with *N,N*-dimethyl formamide. Typically, the molar ratio of the (chloromethylene)dimethylammonium salt to the sucrose-6-ester is about 7:1 to about 11:1.

Subsequently, the hydroxyl groups of the sucrose-6-ester at the 2, 3, 4, 1', 3', 4', and 6' positions are converted to O-alkylformiminium groups. The resulting reaction mixture is heated at a temperature or temperatures and for a period of time or times sufficient to produce a product containing a derivative of sucralose-6-ester in which the remaining hydroxyl groups remain as O-alkylformiminium groups. For example, Walkup, U.S. Pat. No. 4,980,463, the disclosure of which is incorporated herein by reference, and Fry, U.S. 2007/0100139, the disclosure of which is incorporated herein by reference, disclose such processes.

Because formation of a chloroformiminium salt or Vilsmeier reagent is not essential to the chlorination reaction, chlorination agent refers to any compound that can be used to

form a chloroformiminium salt or Vilsmeier reagent, or that can convert the hydroxyl groups of a sucrose-6-ester to chloro groups. Some chlorination agents that can be reacted with a tertiary amide to form a chloroformiminium salt include, for example, phosgene, phosphorus oxychloride, phosphorus pentachloride, thionyl chloride, sulfuryl chloride, oxalyl chloride, trichloromethyl chloroformate ("diphosgene"), bis(trichloromethyl) carbonate ("triphosgene"), and methane sulfonylchloride. Tertiary amides that can be used include, for example, *N,N*-dimethyl formamide (DMF), *N*-formyl piperidine, *N*-formyl morpholine, and *N,N*-diethyl formamide. When *N,N*-dimethyl formamide is used as the tertiary amide, it can also be used as the reaction solvent. Co-solvents can be used at up to about 80 vol% or more of the liquid phase of the reaction medium. Useful co-solvents are those which are both chemically inert and which provide sufficient solvent power to enable the reaction to become essentially homogeneous at the monochlorination stage, for example toluene, o-xylene, 1,1,2-trichloroethane, 1,2-diethoxyethane, and diethylene glycol dimethyl ether.

Quenching of the reaction mixture restores the hydroxyl groups at the 2, 3, 3', and 4' positions and forms the sucralose-6-ester. The reaction mixture can be quenched by the addition of about 0.5 to about 2.0 molar equivalents, typically about 1.0 to about 1.5 molar equivalents, of alkali relative to the amount of chlorination agent used in the reaction. An aqueous solution of an alkali metal hydroxide, such as sodium or potassium hydroxide; an aqueous slurry of an alkaline earth metal hydroxide, such as calcium hydroxide; or aqueous ammonium hydroxide can be used to quench the reaction. For example, an aqueous solution of an alkali metal hydroxide, such as aqueous sodium hydroxide, that contains about 5 wt% to about 35 wt%, typically about 8 wt% to about 20 wt%, and preferably about 10 wt% to about 12 wt% can be used.

As described below, quenching can be carried out by addition of alkali to the reaction mixture, by a dual stream process, or by a circulated process. In each case pH and temperature are controlled during addition of the alkali. Quenching is typically carried out at a pH between about 8.5 to about 10.5 and at a temperature of about 0°C to about 60°C. Preferably, the pH should not be permitted to rise above about 10.5 during the course of the quenching reaction.

In the dual stream process, quenching is carried out by slow addition of the aqueous alkali with simultaneous slow addition of the chlorination reaction material into a reaction vessel. The chlorination reaction mixture and aqueous alkali are simultaneously added slowly until the desired quantity of chlorination reaction mixture has been added. Further aqueous alkali is added until the desired pH is reached. Then the temperature and pH are

maintained at the desired levels for the remainder of the reaction. This process can be a batch or continuous process.

In the circulated process, quenching is carried out by circulating the chlorination reaction mixture from a vessel through a circulation loop. Chlorination reaction mixture and aqueous alkali are added slowly into this circulation loop. Sufficient aqueous alkali is added until the desired pH is reached. Then the temperature and pH are maintained at the desired levels for the remainder of the reaction. This process can be a batch or continuous process.

Following quenching, the reaction mixture can be neutralized by the addition of aqueous acid, for example aqueous hydrochloric acid. The resulting mixture comprises sucralose 6-ester, other carbohydrate including chlorinated carbohydrate impurities, unreacted tertiary amide, and salts in an aqueous solvent in which the predominant solvent is water.

Conversion of Sucralose-6-Ester to Sucralose

The resulting mixture typically comprises both sucralose and sucralose-6-ester. The mixture of sucralose and sucralose-6-ester can be converted to sucralose, and the resulting sucralose purified and isolated by methods known in the art. Methods for hydrolyzing sucralose-6-ester, isolating sucralose, and/or purifying sucralose are disclosed, for example, in Catani, U.S. Pat. Nos. 5,977,349, 6,943,248, 6,998,480, and 7,049,435; Vernon, U.S. Pat. No. 6,890,581; El Kabbani, U.S. Pat. Nos. 6,809,198, and 6,646,121; Navia, U.S. Pat. Nos. 5,298,611 and 5,498,709, and U.S. Pat. Pub. 2004/0030124; Liesen, U.S. Pat. Pub. 2006/0188629 A1; Fry, U.S. Pat. Pub. 2006/0276639 A1; El Kabbani, U.S. Pat. Pub. 2007/0015916 A1; Deshpande, U.S. Pat. Pub. 2007/0160732 A1; and Ratnam, U.S. Pat. Pub. 2007/0270583 A1; the disclosures of which are all incorporated herein by reference.

For example, (a) sucralose-6-ester can be hydrolyzed to sucralose by raising the pH of the reaction mixture to about 11 ± 1 at a temperature and for a time sufficient to effect removal of the protecting group, and (b) the tertiary amide is removed by, for example, steam stripping. Either step (a) or step (b) can be carried out first. Sucralose is recovered from the resulting mixture by batch, continuous, or continuous counter-current extraction of the mixture with an organic solvent, such as dichloromethane, chloroform, 2-butanone, cyclohexanone, ethyl acetate, or a mixture thereof. The organic extract can be decolorized with carbon, concentrated, and seeded with sucralose crystals to precipitate sucralose. The resulting sucralose crystals can be further purified by recrystallization from, for example, water or ethyl acetate. Alternatively, the sucrose can be purified by chromatography.

Purifying sucralose by an initial non-crystallization purification procedure, such as solvent extraction or chromatography, followed by three or more sequential crystallization steps from, for example, water or ethyl acetate, and recycle of the mother liquor remaining from each crystallization step to the feed of another crystallization or purification step is also suitable.

Alternatively, conversion of sucralose-6-ester to sucralose can be carried in methanol containing sodium methoxide. A trans-esterification reaction occurs that forms sucralose and the methyl ester of the acid, for example methyl acetate when the sucralose-6-ester is sucralose-6-acetate. The methyl ester of the acid can be removed by distillation.

INDUSTRIAL APPLICABILITY

The process of the invention is useful in the preparation of sucralose. Sucralose is a high-intensity sweetener that can be used in many food and beverage applications, as well as in other applications. Such applications include, for example, beverages, combination sweeteners, consumer products, sweetener products, tablet cores (Luber, U.S. Pat. No. 6,277,409), pharmaceutical compositions (Luber, U.S. Pat. No. 6,258,381; Roche, U.S. Pat. No. 5,817,340; and McNally, U.S. Pat. No. 5,593,696), rapidly absorbed liquid compositions (Gelotte, U.S. Pat. No. 6,211,246), stable foam compositions (Gowan, Jr., U.S. Pat. No. 6,090,401), dental floss (Ochs, U.S. Pat. No. 6,080,481), rapidly disintegrating pharmaceutical dosage forms (Gowan, Jr., U.S. Pat. No. 5,876,759), beverage concentrates for medicinal purposes (Shah, U.S. Pat. No. 5,674,522), aqueous pharmaceutical suspensions (Ratnaraj, U.S. Pat. No. 5,658,919; Gowan, Jr. U.S. Pat. Nos. 5,621,005 and 5,374,659; and Blase, U.S. Pat. Nos. 5,409,907 and 5,272,137), fruit spreads (Antenucci, U.S. Pat. No. 5,397,588; and Sharp, 5,270,071), liquid concentrate compositions (Antenucci, U.S. Pat. No. 5,384,311), and stabilized sorbic acid solutions (Merciadez, U.S. Pat. No. 5,354,902). The determination of an acceptable sweetness can be accomplished by a variety of standard "taste test" protocols known in the art which are well known to those skilled in the art, such as, for example, the protocols referred to in Merkel, U.S. Pat. No. 6,998,144, and Shamil, U.S. Pat. No. 6,265,012.

The advantageous properties of this invention can be observed by reference to the following examples, which illustrate but do not limit the invention.

Examples

Glossary

DMF *N,N*-dimethyl formamide

DSDA 1,3-diacetoxy-1,1,3,3-tetrabutyl-distannoxane (distannoxane diacetate);
 $(C_4H_9)_2Sn(OAc)-O-Sn(OAc)(C_4H_9)_2$

Example 1

This example demonstrates a process of the invention.

- 5 A 1 liter flask was charged with 25.67 g of sucrose and 550.0 g of DMF, and the sucrose was dissolved at 80°C. After the sucrose had dissolved, 52.07 g of DSDA was added. The water was co-distilled with the DMF using a rotary evaporator with a bath temperature of 80°C for about 1 hr. Final conditions inside the flask were about 70°C and 40 mmHg (5.3 kPa). The resulting product was 124.48 g of light yellow oil.
- 10 The product was diluted with 22.0 g cyclohexane to help keep tin compounds in solution during the acetylation step and acetylated at 2-3°C using 9.22 g of acetic anhydride. Samples were taken and analyzed by high pressure liquid chromatography. At 90 min, the reaction mixture contained sucrose-6-acetate (15.23%; 88.65% normalized), diacetates (1.15%; 6.69% normalized), other monoacetates (0.406%; 2.47% normalized),
- 15 and sucrose (0.377%; 2.19% normalized). These results indicate that the reaction was completed very rapidly. The final quenched product was an almost colorless solution with no visual indication of decomposition.

Example 2

- This example demonstrates a process in which lower temperature dehydration is used.
- 20

- A 1 liter flask was charged with 25.67 g of sucrose and 400 g of DMF. The sucrose was dissolved at 80°C. After the sucrose had dissolved, 48.26 g of DSDA was added. The water was co-distilled with the DMF on a rotary evaporator at a bath temperature of 15°C for about 1 hr. Final conditions inside the flask were about 10°C and <1 mmHg
- 25 (< 0.1 kPa). The product of this step was 173.7 g of colorless oil.

- The product was diluted with 22.0 g of cyclohexane to keep tin compounds in solution during the acetylation step and acetylated at less than 5°C using 9.19 g of acetic anhydride. Samples were taken and analyzed by high pressure liquid chromatography. At 60 min, the reaction mixture contained sucrose-6-acetate (13.22%, 83.1% normalized), diacetates (0.84%; 5.3% normalized), other monoacetates (0.59%; 3.7% normalized),
- 30 sucrose (1.25%; 7.9% normalized). At 135 min, the reaction mixture contained sucrose-6-acetate (13.42%; 84.9% normalized), diacetates (1.20%; 7.6% normalized), other

monoacetates (0.63%; 4.0% normalized), and sucrose (0.549%; 3.5% normalized). The final quenched product was a colorless solution with no visual indication of decomposition.

Example 3

5 This example demonstrates a process in which lower temperature dehydration is used.

A 1 liter flask was charged with 25.67 g of sucrose and 550.0 g of DMF. The sucrose was dissolved at 78°C. After the sucrose had dissolved, 52.0 g of DSDA was added. The water was co-distilled with the DMF on a rotary evaporator at a bath temperature of 60°C for about 1 hr. Final conditions inside the flask were approximately 50°C and 15mmHg
10 absolute (2.0kPa). The product was 167.43 g of a light yellow oil.

The product was diluted with 22.0 g of cyclohexane to keep tin compounds in solution during the acetylation step and acetylated at less than 5°C using 9.19 g of acetic anhydride. Samples were taken and analyzed by high pressure liquid chromatography. At 1 hour, the reaction mixture contained sucrose-6-acetate (14.87%, 87.8% normalized),
15 diacetates (1.21%, 7.0% normalized), other monoacetates (0.50%, 3.0% normalized), and sucrose (0.36%, 2.1% normalized). At 1.5 hours, the reaction mixture contained sucrose-6-acetate (14.83%, 87.4% normalized), diacetates (1.45% 8.6% normalized), other monoacetates (0.50% 3.1% normalized), and sucrose (0.16%, 0.9% normalized). The final
20 quenched product was an almost colorless solution with no visual indication of decomposition.

Example 4

This example demonstrates a process in which lower temperature acetylation is used.

A 1 liter flask was charged with 25.67 g of sucrose and 301.42 g of DMF. The sucrose was dissolved at 80°C. After the sucrose had dissolved, 48.30 g of DSDA was
25 added. The water was co-distilled with the DMF on a rotary evaporator at a bath temperature of 80°C for about 1 hr. Final conditions inside the flask were about 70°C and 40 mmHg absolute (5.3 kPa). The product was 164.39 g of light yellow oil.

The product was diluted with 22.0 g of cyclohexane to keep tin compounds in solution during the acetylation step and acetylated at less than or equal to -20°C using
30 9.19 g of acetic anhydride. Samples were taken and analyzed by high pressure liquid chromatography. After 1 hr, the reaction mixture contained sucrose-6-acetate (12.83%; 78.1% normalized), diacetates (0.591%; 3.5% normalized), other monoacetates (0.46%;

2.7% normalized), sucrose (2.64%; 15.7% normalized). After 4 hrs, the reaction mixture contained sucrose-6-acetate (15.84, 87.2% normalized), diacetates (1.26, 6.9% normalized), other monoacetates (0.54, 3.0% normalized), and sucrose (0.53, 2.9% normalized). These results indicate that the reaction was slower than higher temperature acetylations, but went to similar completion. The final quenched product was an almost colorless solution with no visual indication of decomposition.

Example 5

This example demonstrates a process in which reduced solvent is used and the final high concentration of sucrose-tin adduct is used in acetylation.

A 1 liter flask was charged with 25.67 g of sucrose and 220.0 g of DMF. The sucrose was dissolved at 80°C. After the sucrose has dissolved, 48.36 g of DSDA was added. The water was co-distilled with the DMF on a rotary evaporator at a bath temperature of 80°C for about 0.75 hr. Final conditions inside the flask were about 70°C and 35 mmHg (about 4.7 kPa). The product was 94.20 g of yellow oil.

The product was diluted with 17.5 g of dry DMF and 22.0 g of cyclohexane to keep tin compounds in solution during the acetylation step. The product was acetylated at less than 5°C using 9.19 g of acetic anhydride. Samples were taken and analyzed by high pressure liquid chromatography. After 1 hr, the reaction mixture contained sucrose-6-acetate (23.75%; 87.0% normalized), diacetates (2.19%; 7.9% normalized), other monoacetates (0.71%; 2.7% normalized), and sucrose (0.68%, 2.5% normalized). After 1.5 hr, the reaction mixture contained sucrose-6-acetate (23.34%; 86.6% normalized), diacetates (2.55%; 9.2% normalized), other monoacetates (0.69%; 2.6% normalized), and sucrose (0.42%; 1.5% normalized). The final quenched product was an almost colorless solution with no visual indication of decomposition.

Example 6

This example demonstrates a process in which no co-solvent is added to aid in acetylation.

A 1 liter flask was charged with 25.67 g of sucrose and 250.0 g of DMF. The sucrose was dissolved at 80°C. After the sucrose had dissolved, 48.25 g of DSDA was added. The water was co-distilled with the DMF on a rotary evaporator at a bath temperature of 80°C for about 30 min. Final conditions inside the flask were about 70°C and 40 mmHg (5.3 kPa). The resulting product was 119.09 g of light yellow oil.

The product was acetylated at less than 5°C using 9.19 g of acetic anhydride. Samples were taken and analyzed by high pressure liquid chromatography. At 1 hr, the reaction mixture contained sucrose-6-acetate (20.80%; 87.6% normalized), diacetates (2.00%; 8.42% normalized), other monoacetates (0.67%; 2.80% normalized), and sucrose (0.29%; 1.2% normalized). These results indicate that the reaction was completed very rapidly. The final quenched product was an almost light yellow solution with no visual indication of decomposition.

Example 7

This example demonstrates a process in which solvent-free DSDA is used in dehydration.

A 1 liter flask was charged with 48.25 g of DSDA (containing about 15% cyclohexane to keep as a liquid). The cyclohexane was removed by heating to 80°C and pulling a vacuum down to 40 mmHg. Added to this was 25.67 g of sucrose dissolved in 302.98 g of DMF. The water was co-distilled with the DMF on a rotary evaporator at a bath temperature of 80°C for about 30 min. Final conditions inside the flask were about 70°C and 40 mmHg (5.3 kPa). The resulting product was 160.69 g of light yellow oil.

The product was acetylated at less than 5°C using 9.19 g of acetic anhydride. Samples were taken and analyzed by high pressure liquid chromatography. At 1 hr, the reaction mixture contained sucrose-6-acetate (14.61%; 87.2% normalized), diacetates (1.18%; 7.0% normalized), other monoacetates (0.57%; 3.4% normalized), and sucrose (0.39%; 2.3% normalized). These results indicate that the reaction was completed very rapidly. The final quenched product was an almost light yellow solution with no visual indication of decomposition.

CLAIMS

What is claimed is:

1. A process comprising, in order, the steps of:
 - (a) providing a first reaction mixture comprising sucrose, a polar aprotic solvent
5 and an organotin-based acylation promoter;
 - (b) removing water formed by reaction of sucrose with the organotin-based acylation promoter from the first reaction mixture to afford a second reaction mixture that is substantially free from water, and
 - (c) adding a carboxylic acid anhydride to the second reaction mixture to afford a
10 third reaction mixture, thereby producing a sucrose-6-ester;in which:
a non-polar co-solvent is not added during step (b); and
in step (b), the temperature does not exceed 78°C.
- 15 2. The process of claim 1 in which, during step (b), the removing of water includes distillation of water with the polar aprotic solvent at reduced pressure.
3. The process of claim 1 or claim 2 in which the first reaction mixture and/or the second reaction mixture consist essentially of sucrose, the polar aprotic solvent, the organotin-based acylation promoter, and/or their reaction products.
- 20 4. The process of any preceding claim in which, during step (c), the third reaction mixture is maintained 10°C or less for a period of time sufficient to produce the sucrose-6-ester.
5. The process of any preceding claim in which the temperature in step (b) is between 78°C and 30°C.
- 25 6. The process of any preceding claim in which the temperature in step (b) is between 75°C and 40°C.
7. The process of any preceding claim in which the temperature in step (b) is between 70°C and 50°C.
8. The process of any preceding claim in which the polar aprotic solvent is *N,N*-dimethyl formamide.

9. The process of any preceding claim in which the organotin-based acylation promoter is a 1,3-di(acyloxy)-1,1,3,3-tetra-(hydrocarbyl)distannoxane.

10. The process of any preceding claim in which the organotin-based acylation promoter is 1,3-diacetoxy-1,1,3,3-tetrabutyl-distannoxane.

5 11. The process of any preceding claim in which the carboxylic acid anhydride is acetic anhydride and the sucrose-6-ester is sucrose-6-acetate.

12. The process of any of claims 1 to 10 in which the carboxylic acid anhydride is benzoic anhydride and the sucrose-6-ester is sucrose-6-benzoate.

13. The process of any preceding claim in which the process is a batch process.

10 14. The process of any one of claims 1 to 12 in which the process is a continuous process.

15. The process of any preceding claim additionally comprising, after step (c), the additional step or steps of converting the sucrose-6-ester to sucralose.

FIGURE 1

