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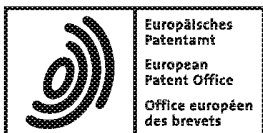
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(54) CHLORINATION OF CARBOHYDRATES AND CARBOHYDRATE DERIVATIVES

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CHLORATION DE GLUCIDES ET DÉRIVÉS DE GLUCIDES

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Description

BACKGROUND OF THE INVENTION

[0001] Chlorination of carbohydrates and derivatives thereof, such as sugars and their esters, has been generally known. For example, chlorination of sucrose to produce sucralose, or 4, ,6'-trichloro-4, ,6'-trideoxygalactosucrose, which is an artificial sweetener with a sweetness intensity many times that of sucrose, has been disclosed in U.S. Patent 4,980,463; WO 2008/052076 A2, U.S. 2007/0100139 A1, and U.S. 2007/0207246 A1. Sucralose can be made by chlorination of a sucrose ester such as sucrose-6-acetate or sucrose-6-benzoate. However, the yields reported in the art for sucralose-6-ester are generally low. For example, the '463 patent discloses examples of preparing sucralose-6-benzoate in molar yields ranging from 31.9% to 60%. WO '076 discloses examples of preparing sucralose-6-acetate in a molar yield of 62.5%. EP 1 923 379 discloses a process for chlorination of organic compounds in a loop reaction.

[0002] The foregoing shows that there exists an unmet need for preparing polychlorinated carbohydrates or derivatives thereof, particularly sucralose-6-ester in high molar yields.

BRIEF SUMMARY OF THE INVENTION

[0003] The invention provides a method for chlorinating a sucrose-6-ester to produce 4,1' 6' -trichloro-4, 1', 6' -trideoxy-6-O-ester of galactosucrose (TGS-6E) in high yields. The method involves recovering and returning at least a portion of the under-chlorinated sucrose-6-ester to a chlorinating step so as to further chlorinate the under-chlorinated sucrose-6-ester to obtain TGS-6E. These recovering and returning steps can be repeated any desired number of times, thereby obtaining high yields.

[0004] Specifically, the invention provides a method for chlorinating a sucrose-6-ester to produce 4,1',6'-trichloro-4,1',6'-trideoxy-6-O-ester of galactosucrose (TGS-6E) of the formula $M-OC(=O)R'$, wherein R' is a hydrophobic group such that TGS-6E has an octanol-water partition coefficient $cLogP$ of 0.5 or greater, and M is the moiety completing the rest of TGS-6E, the method comprising:

(i) reacting the sucrose-6-ester with a chlorinating agent in N,N-dimethylformamide (DMF) to obtain a chlorination reaction mixture, and removing at least a portion of the HCl resulting from the chlorination reaction as a DMF-HCl mixture by vacuum distillation, to obtain a reaction mixture comprising said TGS-6E and at least one under-chlorinated sucrose-6-ester of the formula $M'-OC(=O)R'$, wherein R' is a hydrophobic group such that the under-chlorinated sucrose-6-ester has an octanol-water partition coefficient $cLogP$ of 0.5 or greater, and M' is the moiety

completing the rest of the under-chlorinated sucrose-6- ester;

(ii) returning the at least one under-chlorinated sucrose-6-ester to a chlorinating step and further chlorinating the at least one sucrose-6-ester to obtain TGS-6E; and

(iii) optionally repeating steps (i) and (ii) "n" times where $n \geq 1$.

[0005] The present invention therefore offers one or more of the following advantages: increased yield of TGS-6E, reduced waste stream and/or disposal of the partially or under-chlorinated sucrose-6-ester, potential reduced energy demands, reduced demand for raw materials, and/or improved process economy. The present invention thus provides also an economic advantage over processes known in the art.

DETAILED DESCRIPTION OF THE INVENTION

[0006] In accordance with the inventive method, the TGS-6E can retain the stereochemical configuration of one or more groups on the carbohydrate ring structure or the stereochemical configuration of one or more groups on the carbohydrate ring structure of the TGS-6E could be different than that of the starting sucrose-6-ester.

[0007] The octanol-water partition coefficient (Kow) of $LogP$ or calculated $LogP$ ($cLogP$) describes a compound's propensity to distribute itself between octanol and water: a measurement of how lipophilic and/or hydrophobic it is. When compounds either are not known or are known but their $LogP$ values have not been physically measured, methods of calculating $cLogP$ values are available.

[0008] There are several professional programs that can make the above described calculations which are readily accessible: for example, SciFinder™ offers one - Advanced Chemistry Development (ACD/Labs) Software VI 1.02. There are also freeware resources such as that offered by ChemAxon™.

[0009] In an embodiment of the invention, the TGS-6E or the under chlorinated sucrose-6-ester has an octanol-water partition coefficient $LogP$ or $cLogP$ from about 0.5 to about 3. For reference, monochlorosucrose-6-benzoate ester has a $cLogP$ of 0.7; dichlorogalactosucrose-6-benzoate has a $cLogP$ of 1.5 (interpolated value); 4,1',6'-trichloro- 4,1',6'-trideoxy-6-O-benzoate ester of galactosucrose (TGS6B) has a $cLogP$ of 2.6. 4,1',6'-trichloro-4,1',6'-trideoxy-6-O-acetate ester of galactosucrose (TGS6A) has a $cLogP$ of 0.18, dichlorogalactosucrose-6-acetate ester has a $cLogP$ of 0.06, and monochlorosucrose-6-acetate ester has a $cLogP$ of -0.85.

[0010] In accordance with an embodiment of the inventive method, R' is alkyl, aryl, or arylalkyl, wherein the aryl part of aryl or arylalkyl is optionally substituted with one or more substituents selected from the group consisting of halo, haloalkyl, cyano, nitro, alkoxy, alkylthio,

acyl, acyloxy, thioacyl, acylthio, and aryloxy. In a particular embodiment, R' is aryl, e.g., phenyl, each of which is optionally substituted with one or more substituents selected from the group consisting of halo, haloalkyl, cyano, nitro, alkoxy, alkylthio, acyl, acyloxy, thioacyl, acylthio, and aryloxy. In certain embodiments, R' comprises a hydrophobic polymer. For example, R' could include a hydrophobic or hydrophilic group but in addition a polymer with the net result that R' is hydrophobic.

[0011] Any suitable ester stable to the chlorinating agent, and which can be hydrolyzed, can be used in the present invention. The ester can be a C₁-C₁₈ aliphatic, C₆-C₁₄ aryl C₁-C₁₈ aliphatic or C₆-C₁₄ aryl ester. Particularly suitable carboxylate esters include C₆-C₁₀ aryl carboxylates such as benzoate or naphthoate ester. The ester can be prepared by acylation of the carbohydrate or sugar using an acylating agent of the relevant acid, and in the case of carboxylic acylation, it is an acyl anhydride or acyl halide. Alternatively, the carbohydrate can be esterified by enyl esters.

[0012] The sugar ester is a sucrose-6-ester and the chlorinated product is chlorinated sucrose-6-ester, particularly 4,1',6'-trichloro-4,1',6'-trideoxy-6-O-ester of galactosucrose (TGS-6E). Sucrose-6-ester can be prepared by esterification of sucrose. In accordance with any of the embodiments above, the chlorinating agent employed in the method is an acid chloride or an activated acid chloride. Examples of acid chlorides include thionyl chloride, sulfonyl chloride, phosgene, phosphorus pentachloride, oxalyl chloride, methane sulfonyl chloride, and bis(trichloromethyl)carbonate.

[0013] Examples of activated acid chloride include a Vilsmeier Reagent (also known as Arnold's reagent) having the formula: [XYC=N⁺R₂] Cl⁻, wherein X is hydrogen, aryl, or alkyl, wherein the aryl or alkyl is optionally substituted with a halogen, alkoxy, thioalkoxy, amido, or cyano; Y is a leaving group; and R is hydrogen or alkyl which is optionally substituted with halogen, alkoxy, thioalkoxy, amido, or cyano.

[0014] In accordance with an embodiment, in the formula of the Vilsmeier Reagent, Y is halogen, heteroalkyl, or a group capable of being displaced by a heteroatomic nucleophile, such as tosylate, brosylate, besylate, nosylate, mesylate, alkylfluorosulfonates, triflates, nonaflates, and tresylates, and in a particular example, halogen.

[0015] In accordance with an embodiment, in the formula of the Vilsmeier Reagent, X is hydrogen. In accordance with another embodiment, in the formula of the Vilsmeier Reagent, R and Y are alkyl. In accordance with yet another embodiment, in the formula of the Vilsmeier Reagent, X is hydrogen, Y is chloro, and R is methyl.

[0016] The Vilsmeier Reagent can be produced, for example, by the reaction of an acid chloride with an amide and used either as is or pre-reacted with a heteroatomic nucleophile YH to form an alternative comparably reactive reagent. Such a reagent can alternatively be formed prior to use in the chlorination reaction, or it may be

formed in situ or it may be purchased from commercial sources. In an example, the Vilsmeier Reagent can be produced by the reaction of N,N-dimethylformamide with an acid chloride, for example, an acid chloride selected from the group consisting of thionyl chloride, sulfonyl chloride, phosgene, phosphorus pentachloride, oxalyl chloride, methane sulfonyl chloride, and bis(trichloromethyl)carbonate.

[0017] The chlorination reaction is carried out in a solvent system comprising an N,N-dimethylformamide. The solvent system may comprise a mixture of N,N-dimethylformamide a polar aprotic solvent and at least one other aprotic solvent selected from the group consisting of chlorinated hydrocarbons and ethers. Examples of chlorinated hydrocarbons are chloroform, dichloromethane, dichloroethane, chlorofluorocarbons, dichloroethylene, trichloroethylene, trichloropropane, trichloroethane, dichloroethane, tetrachloroethane, and perfluorooctane, and mixtures thereof. In an embodiment, the ether is selected from the group consisting of tetrahydrofuran, dioxane, methoxyethane, dimethoxymethane, dimethoxyethane, tetrahydropyran, diglyme, diisopropyl ether, diethyl ether, and methyl t-butyl ether, and mixtures thereof.

[0018] For example, the sucrose-6-ester and the chlorinating agent are combined in the solvent at a suitable temperature, for example, between -30 °C and 25 °C. During the addition of the chlorinating agent, the temperature is generally not allowed to rise above about 60 °C, and in embodiments, above 50 °C. Typically, the temperature is maintained from about 0 °C to about 30 °C. At least a portion of the HCl formed during the chlorination is removed by applying vacuum.

[0019] The chlorinating agent and the sucrose-6-ester to be chlorinated can be reacted in a suitable ratio, for example, in a ratio of 5 to 10 molar equivalents, preferably 7 to 8 molar equivalents of acid chloride.

[0020] In any of the above embodiments, the method can further include the step of (iv) quenching at least a portion of the reaction mixture obtained in step (i) to obtain a quenched reaction mixture. In accordance with the invention, the quenching step can be carried out by any suitable method, for example, by pouring the reaction mixture, preferably a cooled reaction mixture, e.g., at 5 °C, into a cold basic solution such as aqueous alkali metal hydroxide, e.g., sodium or potassium hydroxide, an aqueous slurry of alkaline earth metal oxide or hydroxide, such as calcium oxide or hydroxide, aqueous ammonium hydroxide solution, or pyridine/methanol solution.

[0021] The quenched reaction mixture contains chlorinated sucrose-6-esters, e.g., a mixture of TGS-6E and one or more of the under-chlorinated sucrose-6-esters.

[0022] In accordance with an embodiment, the inventive method can further include the step of (v) isolating a product mixture comprising TGS-6E and at least one under-chlorinated sucrose-6-ester from the quenched reaction mixture. The product mixture can be isolated by any suitable method known to those skilled in the art, for

example, by solvent or solid phase extraction, chromatographic methods, crystallization, filtration, or any other method suitable for separating the desired mixture from the undesirable solvents and/or impurities.

[0023] In the method, the at least one under-chlorinated sucrose-6-ester is returned to a chlorination step, e.g., to step (i), to further chlorinate the under-chlorinated sucrose-6-ester. When the under-chlorinated sucrose-6-ester is returned to the chlorination step, the under-chlorinated sucrose-6-ester could be returned as a particular under-chlorinated sucrose-6-ester, as a mixture of under-chlorinated sucrose-6-esters, or as a mixture of the under-chlorinated sucrose-6-ester with other materials, for example, TGS-6E.

[0024] In accordance with an embodiment of the method, the further chlorination of the at least one under-chlorinated sucrose-6-ester takes place in a vessel separate from the vessel where step (i) takes place.

[0025] In accordance with an embodiment of the method, the further chlorination of the at least one under-chlorinated sucrose-6-ester takes place in the same vessel where step (i) takes place.

[0026] In any of the embodiments, the method is a continuous feed method.

[0027] In any of the embodiments described above, the TGS-6E, e.g., sucralose-6-ester, is obtained in step (i) in a yield of at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, on a molar basis and/or on a mass basis.

[0028] In any of the embodiments described above, the TGS-6E, e.g., sucralose-6-ester, is obtained in step (iii) in a yield of at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, on a molar basis and/or on a mass basis.

[0029] In accordance with an embodiment of the method, the product mixture is isolated from the quenched reaction mixture by solvent extraction. The solvent used for the extraction is preferably a water immiscible solvent, for example, ethyl acetate, halocarbons, or any other solvent which forms a biphasic hydrophobic (organic) layer with a hydrophilic (aqueous) layer which enables partitioning and physical extractive separation of the desired product mixture from other impurities. This does not exclude incomplete partitioning, wherein some product remains partially dissolved in the aqueous layer requiring subsequent extractions. This also does not exclude incomplete partitioning, wherein some organic solvent is partially dissolved in the aqueous layer (e.g. DMF, DMA, ethyl acetate, etc.) nor the organic solvent partially dissolve in the aqueous layer (e.g. water, alcohols, etc.). The extract can be optionally decolorized to remove undesirable colored impurities.

Decolorization can be carried out by any suitable method, for example, by treating with activated carbon.

[0030] In accordance with an embodiment of the invention, the method can further include the step of (vi) separating the product mixture isolated in step (v) into (a) a first fraction comprising the TGS-6E and (b) a sec-

ond fraction comprising at least one under-chlorinated sucrose-6-ester. The separation can be carried out by any suitable method, for example, solvent extraction taking advantage of the differing solubility properties of the TGS-6E relative to the under-chlorinated sucrose-6-ester.

[0031] The first fraction can contain only the TGS-6E or a mixture of the TGS-6E and at least one under-chlorinated sucrose-6-ester; however, when it is a mixture of TGS-6E and at least one under-chlorinated sucrose-6-ester, the first fraction contains an excess amount of the TGS-6E relative to the under-chlorinated sucrose-6-ester.

[0032] The second fraction contains at least one under-chlorinated sucrose-6-ester. The second fraction can contain only one or more under-chlorinated sucrose-6-esters, or it can contain a mixture of one or more under-chlorinated sucrose-6-esters and TGS-6E; however, when it is a mixture of under-chlorinated sucrose-6-ester and TGS-6E, the second fraction contains an excess amount of the under-chlorinated sucrose-6-ester relative to the TGS-6E.

[0033] In accordance with an embodiment of the invention, the TGS-6E, the under-chlorinated sucrose-6-ester, or a mixture thereof, is optionally combined with additional sucrose-6-ester and returned to another chlorinating step, e.g., step (i) of the method, for further chlorination of the under-chlorinated sucrose-6-ester and optionally, chlorination of the additional sucrose-6-ester.

[0034] In a specific embodiment, the invention provides a method for chlorinating a sucrose-6-ester to obtain TGS-6E as defined above, the method comprising:

- (i) dissolving the sucrose-6-ester in N,N-dimethylformamide to obtain a solution comprising the sucrose-6-ester;
- (ii) combining the solution comprising the sucrose-6-ester from step (i) with a chlorinating agent to obtain a chlorination mixture;
- (iii) heating the chlorination mixture to obtain a mixture of chlorinated sucrose-6-esters comprising the desired TGS-6E and at least one under-chlorinated sucrose-6-ester having less than the desired number of chlorine atoms;
- (iv) returning at least one under-chlorinated sucrose-6-ester to a chlorinating step so as to further chlorinate the at least one under-chlorinated sucrose-6-ester; and optionally
- (v) repeating steps (ii)-(iv) "n" times where $n \geq 1$.

[0035] The above method can further include a step of (vi) separating the TGS-6E thereof from the at least one under-chlorinated sucrose-6-ester.

[0036] In accordance with an embodiment of the above method, the at least one under-chlorinated sucrose-6-ester is returned to step (i) for further chlorination.

[0037] In accordance with an embodiment of the above method, the further chlorination of the at least one under-

chlorinated sucrose-6-ester takes place in a vessel separate from the vessel where step (i) takes place.

[0038] In accordance with an embodiment of the above method, the further chlorination of the at least one under-chlorinated sucrose-6-ester takes place in the same vessel where step (i) takes place.

[0039] In any of the embodiments, the above method is a continuous feed method.

[0040] In accordance with any of the embodiments above, the under-chlorinated sucrose-6-ester has one or two chlorine atoms in its molecular structure. In accordance with any of the embodiments above, the desired number of chlorine atoms present in the TGS-6E is 3.

[0041] In any of the embodiments described above, the chlorination reaction followed by recovering and returning the under-chlorinated sucrose-6-ester can be repeated any number of times, and in a particular embodiment, to reach a steady state. In an embodiment, the recovering and returning can be performed for a "n" value in step (iii) or (v) of 2 to 8, 3 to 7, 4 to 6, or 5.

[0042] In any of the embodiments, in addition to recovering and returning the under-chlorinated sucrose-6-ester to the original chlorination step, additional sucrose-6-ester can be combined with the returning under-chlorinated sucrose-6-ester.

[0043] In any of the embodiments described above, the sucralose-6-ester is obtained in step (i) in an yield of at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, on a molar basis and/or on a mass basis.

[0044] In any of the embodiments described above, the sucralose-6-ester is obtained in step (v) in an yield of at least 50%, at least 60%, at least 70%, at least 80%, or at least 90%, on a molar basis and/or on a mass basis.

[0045] Sucralose may be prepared by a method comprising de-esterifying the TGS-6E obtained in accordance with any of the embodiments above to obtain sucralose. For example, de-esterification can be carried out by alkaline hydrolysis of the ester; see, e.g., US '463, col. 9, lines 4-40 and Example 16.

EXAMPLE

[0046] This example demonstrates a method of preparing sucralose in accordance with an embodiment of the invention. 0.05 mole sucrose-6-benzoate (S6B) (22.6 grams) was taken up in 850 mL of anhydrous N,N-dimethylformamide (DMF), pre-distilled under full vacuum to constant temperature (41 °C, 75 mL distillate). The DMF solution was cooled to 5 °C (icebath) and 0.4 mole Vilsmeier (8 equivalents, 52 grams) was added. The resulting pale yellow suspension was stirred and warmed to ambient temperature over 30 min and then heated to 60 °C for 3 hours at which time, the suspension became a pale orange homogeneous solution. TLC analysis showed no more S6B was present. After cooling the solution, 600 mL of DMF-HCl (ca. 0.4 M) formed during the chlorination reaction was distilled off under full vacuum. The resulting

reaction mixture was then heated to 87 °C for 8 hours. The reaction mixture was cooled to 5 °C and poured into 500 mL cold aqueous ammonium hydroxide. The resulting mixture was extracted with ethyl acetate (2 x 500 mL) to extract the 4,1',6'-trichloro-4,1',6'-trideoxy-6-O-benzoate ester of galactosucrose and any partially or under-chlorinated sucrose products. The extract was decolorized by stirring with activated carbon (10 g), and the extract was filtered through celite and concentrated under vacuum. The residue obtained was dissolved in ethyl acetate (100 mL) and washed with brine (2x50 mL) to remove the residual DMF. The resulting product was dried under vacuum for 30 min to remove further DMF and 19 grams of an amorphous foamy solid were obtained. The foamy solid was then dissolved in a mixture of methyl t-butyl ether (150 mL) and water (5 mL). TGS6B (13.9 g, 62% yield by mass, >95% purity) precipitated as an off-white solid upon vigorous stirring over 30 min and was collected by filtration. The filtrate (mother liquor) was concentrated to 8 grams.

[0047] The above procedure was repeated to scale on the 8 grams of mother liquor with the following exceptions: (175 mL DMF initial volume, 15 mL predistillation, 7 eq Vilsmeier, 20 g), and the reaction was held at 60 °C for only 30 min, and 125 mL of DMF was distilled off for the second distillation. This iteration provided another batch of TGS6B (4.1 g, 18% yield by mass, >95% pure) for a combined yield of 80% by mass. Another 3 grams of mother liquor containing ca. 1 : 1 mixture of di- and/or tri-chlorinated sucrose ester and the same amount of the original higher Rf material was also recovered. Each chlorination reaction was conducted for 8-10 hours at 87 °C.

[0048] The yields obtained are as follows: 1st iteration: 56% molar, 62% mass; 2nd iteration: 16.5% molar, 18% mass (based on original reaction); and the combined yield from the two iterations were: 72.5% molar, 80% mass. If the mother liquor was included, the combined yield was 84% molar, 93% mass.

Claims

1. A method for chlorinating a sucrose-6-ester to produce 4,1',6'-trichloro-4,1',6'-trideoxy-6-O-ester of galactosucrose (TGS-6E) of the formula M-OC(=O)R', wherein R' is a hydrophobic group such that TGS-6E has an octanol-water partition coefficient cLogP of 0.5 or greater, and M is the moiety completing the rest of TGS-6E, the method comprising:

(i) reacting the sucrose-6-ester with a chlorinating agent in N,N-dimethylformamide (DMF) to obtain a chlorination reaction mixture, and removing at least a portion of the HCl resulting from the chlorination reaction as a DMF-HCl mixture by vacuum distillation, to obtain a reac-

- tion mixture comprising said TGS-6E and at least one under-chlorinated sucrose-6-ester of the formula $M'-OC(=O)R'$, wherein R' is a hydrophobic group such that the under-chlorinated sucrose-6-ester has an octanol-water partition coefficient $cLogP$ of 0.5 or greater, and M' is the moiety completing the rest of the under-chlorinated sucrose-6-ester;
- (ii) returning the at least one under-chlorinated sucrose-6-ester to a chlorinating step and further chlorinating the at least one sucrose-6-ester to obtain TGS-6E; and
- (iii) optionally repeating steps (i) and (ii) "n" times where $n \geq 1$.
2. The method of claim 1, further comprising:
- (iv) quenching at least a portion of the reaction mixture from step (i) to obtain a quenched reaction mixture and
- (v) isolating a product mixture comprising TGS-6E and at least one under-chlorinated sucrose-6-ester from the quenched reaction mixture.
3. The method of claim 1, wherein;
- (a) the at least one under-chlorinated sucrose-6-ester is returned to step (i) for further chlorination; or
- (b) wherein the further chlorination of the at least one under-chlorinated sucrose-6-ester takes place in a vessel separate from the vessel where step (i) takes place; or
- (c) wherein the further chlorination of the at least one under-chlorinated sucrose-6-ester takes place in the same vessel where step (i) takes place.
4. The method of claim 2, wherein in step (v), the product mixture is isolated from the quenched reaction mixture by solvent extraction; and/or the method comprises (vi) separating the product mixture isolated in step (v) into (a) a first fraction comprising TGS-6E and (b) a second fraction comprising at least one under-chlorinated sucrose-6-ester.
5. The method of any one of claims 1 to 4, wherein TGS-6E, the at least one under-chlorinated sucrose-6-ester, or a mixture thereof, is optionally combined with additional sucrose-6-ester and returned to a chlorinating step or to step (i).
6. The method of any one of claims 1 to 5, wherein R' is phenyl.
7. The method of any one of claims 1 to 6, wherein the chlorinating agent is an acid chloride, an activated acid chloride, or bis(trichloromethyl)carbonate, preferably wherein the acid chloride is selected from the group consisting of thionyl chloride, sulfonyl chloride, phosgene, phosphorus pentachloride, oxalyl chloride, and methanesulfonyl chloride, and wherein the activated acid chloride is a Vilsmeier Reagent having the formula: $[XYC=N^+R_2] Cl^-$, wherein X is hydrogen, aryl, or alkyl, wherein the aryl or alkyl is optionally substituted with a halogen, alkoxy, thioalkoxy, amido, or cyano; Y is a leaving group, preferably Y is halogen, heteroalkyl, or a group capable of being displaced by a heteroatomic nucleophile; and R is hydrogen or alkyl which is optionally substituted with halogen, alkoxy, thioalkoxy, amido, or cyano.
8. The method of claim 7, wherein X is hydrogen, Y is chloro, and R is methyl.
9. The method according to claim 1, wherein the TGS-6E is sucrose-6-benzoate ester (TGS-6B), the method comprising:
- (a) dissolving the sucrose-6-benzoate ester in N,N-dimethylformamide (DMF) to obtain a solution comprising the sucrose-6-benzoate ester;
- (b) combining the solution comprising the sucrose-6-benzoate ester from step (i) with a chlorinating agent to obtain a chlorination mixture;
- (c) removing by vacuum distillation at least a portion of the HCl resulting from the chlorination reaction as a DMF-HCl mixture to obtain a reaction mixture comprising TGS-6B and at least one under-chlorinated sucrose-6-benzoate ester;
- (d) returning the at least one under-chlorinated sucrose-6-benzoate ester to a chlorinating step so as to further chlorinate the at least one under-chlorinated sucrose-6-benzoate ester; and optionally
- (e) repeating steps (b)-(d) "n" times where $n \geq 1$.
10. The method of claim 9, further comprising (f) separating the TGS-6B from the at least one under-chlorinated sucrose-6-benzoate ester.
11. The method of claim 9, wherein the at least one under-chlorinated sucrose-6-benzoate ester is returned to step (a) for further chlorination.
12. The method of claim 1 to 11, wherein $n = 2$ to 8.
13. The method of claim 1 or 9, wherein the at least one under-chlorinated sucrose-6-ester is dichlorogalactosucrose-6-benzoate.
14. The method of claim 1 or 9, wherein the at least one under-chlorinated sucrose-6-ester is monochlorosucrose-6-benzoate.

Patentansprüche

1. Verfahren zur Chlorierung eines Sucrose-6-esters zur Herstellung von 4,1',6'-Trichlor-4,1',6'-tridesoxy-6-0-ester der Galactosucrose (TGS-6E) der Formel $M-OC(=O)R'$, wobei R' eine hydrophobe Gruppe ist, so dass TGS-6E einen Octanol-Wasser-Partitionskoeffizienten $cLogP$ von 0,5 oder höher aufweist, und M die Baugruppe ist, welche den Rest von TGS-6E komplettiert, wobei das Verfahren umfasst:

(i) Umsetzen des Sucrose-6-esters mit einem Chlorierungsmittel in N,N-Dimethylformamid (DMF) unter Erhalt eines Chlorierungsreaktionsgemisches, und Entfernen wenigstens eines Teils des aus der Chlorierungsreaktion resultierenden HCl als ein DMF-HCl-Gemisch durch Vakuumdestillation, unter Erhalt eines Reaktionsgemisches, umfassend das TGS-6E und wenigstens einen unterchlorierten Sucrose-6-ester der Formel $M'-OC(=O)R'$, wobei R' eine hydrophobe Gruppe ist, so dass der unterchlorierte Sucrose-6-ester einen Octanol-Wasser-Partitionskoeffizienten $cLogP$ von 0,5 oder höher aufweist, und M' die Baugruppe ist, die den Rest des unterchlorierten Sucrose-6-esters komplettiert;

(ii) Rückführen des wenigstens einen unterchlorierten Sucrose-6-esters in einen Chlorierungsschritt und weiteres Chlorieren des wenigstens einen Sucrose-6-esters unter Erhalt von TGS-6E; und

(iii) gegebenenfalls Wiederholen der Schritte (i) und (ii) n-mal, wobei $n \geq 1$ ist.

2. Verfahren gemäß Anspruch 1, des Weiteren umfassend:

(iv) Quenchen wenigstens eines Teils des Reaktionsgemisches aus Schritt (i) unter Erhalt eines gequenchten Reaktionsgemisches, und
(v) Isolieren eines Produktgemisches, umfassend TGS-6E und wenigstens einen unterchlorierten Sucrose-6-ester, aus dem gequenchten Reaktionsgemisch.

3. Verfahren gemäß Anspruch 1, wobei:

(a) der wenigstens eine unterchlorierte Sucrose-6-ester in den Schritt (i) zur weiteren Chlorierung rückgeführt wird; oder

(b) wobei die weitere Chlorierung des wenigstens einen unterchlorierten Sucrose-6-esters in einem von dem Gefäß, in welchem Schritt (i) stattfindet, getrennten Gefäß stattfindet; oder

(c) wobei die weitere Chlorierung des wenigstens einen unterchlorierten Sucrose-6-esters in demselben Gefäß stattfindet, in welchem Schritt

(i) stattfindet.

4. Verfahren gemäß Anspruch 2, wobei im Schritt (v) das Produktgemisch aus dem gequenchten Reaktionsgemisch durch Lösungsmittlextraktion isoliert wird; und/oder das Verfahren (vi) das Abtrennen des in Schritt (v) isolierten Produktgemisches in (a) eine erste Fraktion, welche TGS-6E umfasst, und (b) eine zweite Fraktion, welche wenigstens einen unterchlorierten Sucrose-6-ester umfasst, umfasst.

5. Verfahren gemäß einem der Ansprüche 1 bis 4, wobei TGS-6E, der wenigstens eine unterchlorierte Sucrose-6-ester oder ein Gemisch davon gegebenenfalls mit zusätzlichem Sucrose-6-ester vereinigt wird und in einen Chlorierungsschritt oder in Schritt (i) rückgeführt wird.

6. Verfahren gemäß einem der Ansprüche 1 bis 5, wobei R' Phenyl ist.

7. Verfahren gemäß einem der Ansprüche 1 bis 6, wobei das Chlorierungsmittel ein Säurechlorid, ein aktiviertes Säurechlorid oder Bis(trichlormethyl)carbonat ist, wobei vorzugsweise das Säurechlorid ausgewählt ist aus der Gruppe, bestehend aus Thionylchlorid, Sulfurylchlorid, Phosgen, Phosphorpentachlorid, Oxalylchlorid und Methansulfonylchlorid, und wobei das aktivierte Säurechlorid ein Vilsmeier-Reagens ist mit der Formel $[XYC=N^+R_2]Cl^-$, wobei X Wasserstoff, Aryl oder Alkyl ist, wobei das Aryl oder Alkyl gegebenenfalls mit einem Halogen, Alkoxy, Thioalkoxy, Amido oder Cyano substituiert ist; Y eine Abgangsgruppe ist, vorzugsweise Y Halogen, Heteroalkyl oder eine Gruppe ist, die in der Lage ist, dass sie durch ein heteroatomares Nucleophil ersetzt wird; und R Wasserstoff oder Alkyl ist, welches gegebenenfalls mit Halogen, Alkoxy, Thioalkoxy, Amido oder Cyano substituiert ist.

8. Verfahren gemäß Anspruch 7, wobei X Wasserstoff ist, Y Chlor ist und R Methyl ist.

9. Verfahren gemäß Anspruch 1, wobei TGS-6E Sucrose-6-benzoatester (TGS-6B) ist, wobei das Verfahren umfasst:

(a) Lösen des Sucrose-6-benzoatesters in N,N-Dimethylformamid (DMF) unter Erhalt einer Lösung, welche den Sucrose-6-benzoatester umfasst;

(b) Vereinigen der Lösung, welche den Sucrose-6-benzoatester aus Schritt (i) umfasst, mit einem Chlorierungsmittel unter Erhalt eines Chlorierungsgemisches;

(c) Entfernen wenigstens eines Teils des HCl, der aus der Chlorierungsreaktion stammt, als ein DMF-HCl-Gemisch durch Vakuumdestillation

- on unter Erhalt eines Reaktionsgemisches, umfassend TGS-6B und wenigstens einen unterchlorierten Sucrose-6-benzoatester;
- (d) Rückführen des wenigstens einen unterchlorierten Sucrose-6-benzoatesters in einen Chlorierungsschritt, um so den wenigstens einen unterchlorierten Sucrose-6-benzoatester weiter zu chlorieren; und gegebenenfalls
- (e) Wiederholen der Schritte (b)-(d) n-mal, wobei $n \geq 1$ ist.
10. Verfahren gemäß Anspruch 9, des Weiteren umfassend (f) Abtrennen des TGS-6B aus dem wenigstens einen unterchlorierten Sucrose-6-benzoatester.
11. Verfahren gemäß Anspruch 9, wobei der wenigstens eine unterchlorierte Sucrose-6-benzoatester in den Schritt (a) zur weiteren Chlorierung rückgeführt wird.
12. Verfahren gemäß Anspruch 1 bis 11, wobei $n = 2$ bis 8.
13. Verfahren gemäß Anspruch 1 oder 9, wobei der wenigstens eine unterchlorierte Sucrose-6-ester Dichlorgalactosucrose-6-benzoat ist.
14. Verfahren gemäß Anspruch 1 oder 9, wobei der wenigstens eine unterchlorierte Sucrose-6-ester Monochlorsucrose-6-benzoat ist.
- Revendications**
1. Procédé de chloration d'un 6-ester de saccharose pour produire un 4,1',6'-trichloro-4,1',6'-tridésoxy-6-O-ester de galactosaccharose (TGS-6E), de formule $M-OC(=O)R'$, dans laquelle R' représente un groupe hydrophobe tel que le TGS-6E présente un coefficient de partage octanol/eau $cLogP$ valant 0,5 ou plus, et M représente le fragment qui complète le reste du TGS-6E, lequel procédé comporte les étapes suivantes :
- i) faire réagir le 6-ester de saccharose avec un agent de chloration, dans du N,N-diméthyl-formamide (DMF), ce qui donne un mélange réactionnel de chloration, et éliminer par distillation sous vide au moins une partie du chlorure d'hydrogène (HCl) résultant de la réaction de chloration, sous la forme d'un mélange DMF-HCl, pour obtenir un mélange réactionnel comprenant ledit TGS-6E et au moins un 6-ester de saccharose sous-chloré, de formule $M'-OC(=O)R'$, dans laquelle R' représente un groupe hydrophobe tel que le 6-ester de saccharose sous-chloré présente un coefficient de partage octanol/eau $cLogP$ valant 0,5 ou plus, et M' représente le fragment qui complète le reste du 6-ester de saccharose sous-chloré ;
- ii) renvoyer le 6-ester de saccharose sous-chloré, au nombre d'au moins un, vers une étape de chloration et poursuivre la chloration de ce 6-ester de saccharose sous-chloré, au nombre d'au moins un, pour en faire du TGS-6E ;
- iii) et en option, répéter n fois les étapes (i) et (ii), étant entendu que n est supérieur ou égal à 1.
2. Procédé conforme à la revendication 1, qui comporte en outre les étapes suivantes :
- iv) arrêter la réaction dans au moins une partie du mélange réactionnel issu de l'étape (i), pour obtenir un mélange réactionnel bloqué ;
- v) et isoler, à partir de ce mélange réactionnel bloqué, un mélange de produits comprenant du TGS-6E et au moins un 6-ester de saccharose sous-chloré.
3. Procédé conforme à la revendication 1, dans lequel
- a) le 6-ester de saccharose sous-chloré, au nombre d'au moins un, est renvoyé vers l'étape (i) pour la poursuite de la chloration ;
- b) ou la poursuite de la chloration du 6-ester de saccharose sous-chloré, au nombre d'au moins un, a lieu dans un récipient distinct de celui où se déroule l'étape (i) ;
- c) ou la poursuite de la chloration du 6-ester de saccharose sous-chloré, au nombre d'au moins un, a lieu dans le même récipient que celui où se déroule l'étape (i).
4. Procédé conforme à la revendication 2, dans lequel, dans l'étape (v), le mélange de produits est isolé, à partir du mélange réactionnel bloqué, par extraction à l'aide d'un solvant, et/ou lequel procédé comporte une étape (vi) de séparation du mélange de produits isolé dans l'étape (v) en les fractions suivantes :
- a) une première fraction comprenant du TGS-6E,
- b) et une deuxième fraction comprenant au moins un 6-ester de saccharose sous-chloré.
5. Procédé conforme à l'une des revendications 1 à 4, dans lequel le TGS-6E, le 6-ester de saccharose sous-chloré, au nombre d'au moins un, ou un mélange de ces derniers, est, en option, combiné avec un supplément de 6-ester de saccharose et renvoyé vers une étape de chloration ou vers l'étape (i).
6. Procédé conforme à l'une des revendications 1 à 5, dans lequel R' représente un groupe phényle.
7. Procédé conforme à l'une des revendications 1 à 6,

dans lequel l'agent de chloration est un chlorure d'acide, un chlorure d'acide activé, ou du carbonate de bis(trichloro-méthyle), lequel chlorure d'acide est de préférence choisi dans l'ensemble constitué par les chlorure de thionyle, chlorure de sulfuryle, phosphogène, pentachlorure de phosphore, chlorure d'oxalyle et chlorure de méthanesulfonyle, et lequel chlorure d'acide activé est un réactif de Vilsmeier, de formule $[CYC=N^+R^2].Cl^-$, dans laquelle

- X représente un atome d'hydrogène ou un groupe aryle ou alkyle, lequel groupe aryle ou alkyle, en option, porte un ou des substituant(s) halogéno, alcoxy, alkylthio, amido ou cyano,
- Y représente un groupe partant, étant entendu que, de préférence, Y représente un atome d'halogène, un groupe hétéroalkyle ou un groupe qui peut être déplacé par un nucléophile hétéroatomique,
- et R représente un atome d'hydrogène ou un groupe alkyle qui, en option, porte un ou des substituant(s) halogéno, alcoxy, alkylthio, amido ou cyano.

8. Procédé conforme à la revendication 7, dans lequel X représente un atome d'hydrogène, Y représente un atome de chlore et R représente un groupe méthyle. 25
9. Procédé conforme à la revendication 1, dans lequel le TGS-6E est de l'ester 6-benzoate de saccharose (TGS-6B), et lequel procédé comporte les étapes suivantes : 30
 - a) dissoudre l'ester 6-benzoate de saccharose dans du N,N-diméthyl-formamide (DMF), pour en faire une solution contenant l'ester 6-benzoate de saccharose ; 35
 - b) combiner la solution contenant l'ester 6-benzoate de saccharose, issue de l'étape (a), avec un agent de chloration, pour en faire un mélange de chloration ; 40
 - c) éliminer par distillation sous vide au moins une partie du chlorure d'hydrogène (HCl) résultant de la réaction de chloration, sous la forme d'un mélange DMF-HCl, pour obtenir un mélange réactionnel comprenant du TGS-6B et au moins un ester 6-benzoate de saccharose sous-chloré ; 45
 - d) renvoyer l'ester 6-benzoate de saccharose sous-chloré, au nombre d'au moins un, vers une étape de chloration, pour poursuivre la chloration de cet ester 6-benzoate de saccharose sous-chloré, au nombre d'au moins un ; 50
 - e) et en option, répéter n fois les étapes (b) à (d), étant entendu que n est supérieur ou égal à 1. 55

10. Procédé conforme à la revendication 9, qui comporte en outre une étape (f) de séparation du TGS-6B d'avec l'ester 6-benzoate de saccharose sous-chloré, au nombre d'au moins un.

11. Procédé conforme à la revendication 9, dans lequel l'ester 6-benzoate de saccharose sous-chloré, au nombre d'au moins un, est renvoyé vers l'étape (a) pour la poursuite de la chloration.

12. Procédé conforme à l'une des revendications 1 à 11, dans lequel n vaut de 2 à 8.

13. Procédé conforme à la revendication 1 ou 9, dans lequel le 6-ester de saccharose sous-chloré, au nombre d'au moins un, est un 6-benzoate de dichloro-galacto-saccharose.

14. Procédé conforme à la revendication 1 ou 9, dans lequel le 6-ester de saccharose sous-chloré, au nombre d'au moins un, est un 6-benzoate de monochloro-galacto-saccharose.

REFERENCES CITED IN THE DESCRIPTION

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Szénhidrátok klórozása és szénhidrát származékok

SZABADALMI IGÉNYPONTOK

1. Eljárás egy szacharóz-6-észter klórozására, $M-OC(=O)R'$ képletű galakto-szacharóz 4,1',6'-triklór-4,1',6'-tridezoxi-6-O-észterének (TGS-6E) előállítására, ahol R' egy olyan hidrofób csoport, hogy a TGS-6E $cLogP$, oktanol-víz partíciós együtthatója 0,5 vagy ennél nagyobb, és M egy atomcsoport, amely kiegészíti a TGS-6E fennmaradt részét, amely eljárás magában foglalja:

- (i) a szacharóz-6-észternek egy klórozó-szerrel való reagáltatását N,N -dimetil-formamidban (DMF), amellyel egy klórozó reakciókeveréket kapunk, és a klórozási reakcióból DMF-HCl keverékként keletkező HCl legalább egy részének vákuum-desztillálással való eltávolítását, amellyel a TGS-6E-t és legalább egy $M'-OC(=O)R'$ képletű aluklórozott szacharóz-6-észtert kapunk, ahol az R' egy olyan hidrofób csoport, hogy az aluklórozott szacharóz-6-észter $cLogP$, oktanol-víz partíciós együtthatója 0,5 vagy ennél nagyobb, és M' egy atomcsoport, amely kiegészíti az aluklórozott szacharóz-6-észter maradék részét;
- (ii) a legalább egy aluklórozott szacharóz-6-észternek egy klórozó lépésbe való visszavezetését, és a legalább egy szacharóz-6-észternek a továbbklórozását, amellyel a TGS-6E-t kapjuk; és
- (iii) adott esetben az (i) és (ii) lépések "n" alkalommal való ismétlését, ahol $n \geq 1$.

2. Az 1. igénypont szerinti eljárás, amely továbbá magában foglalja

- (iv) az (i) lépésből származó reakciókeverék legalább egy részének a kvencselését, amellyel egy kvencselt reakciókeveréket kapunk, és
- (v) egy, TGS-6E-t és legalább egy aluklórozott szacharóz-6-észtert tartalmazó termékelegynek az izolálását a kvencselt reakciókeverékből.

3. Az 1. igénypont szerinti eljárás, amelyben

- (a) a legalább egy aluklórozott szacharóz-6-észtert továbbklórozás céljából visszavezetjük az (i) lépésbe; vagy
- (b) ahol a legalább egy aluklórozott szacharóz-6-észter továbbklórozását egy olyan tartályban valósítjuk meg, amely eltér attól a tartálytól, amelyben az (i) lépést valósítjuk meg; vagy

(c) ahol a legalább egy alulklórozott szacharóz-6-észter továbbklórozását egy olyan tartályban valósítjuk meg, amely azonos azzal, amelyben az (i) lépést valósítjuk meg.

4. A 2. igénypont szerinti eljárás, amelyben az (v) lépésben, a termékelegyet a kvencselt reakciókeveréktől egy oldószeres extrakcióval választjuk el; és/vagy az eljárás magában foglalja (vi) az (v) lépésben izolált termékelegy elválasztását (a) egy, a TGS-6E-t tartalmazó első frakcióba és (b) egy, a legalább egy alulklórozott szacharóz-6-észtert tartalmazó második frakcióba.

5. Az 1-4. igénypontok egyike szerinti eljárás, amelyben a TGS-6E-t, a legalább egy alulklórozott szacharóz-6-észtert, vagy ezek egy keverékét, adott esetben egy további szacharóz-6-észterrel kombináljuk, és visszavezetjük egy klórozó lépésbe vagy az (i) lépésbe.

6. Az 1-5. igénypontok egyike szerinti eljárás, amelyben az R' jelentése fenil-csoport.

7. Az 1-6. igénypontok egyike szerinti eljárás, amelyben a klórozó-szer egy savklorid, egy aktivált savklorid vagy bisz(triklór-metil)karbonát, előnyösen amelyben a savkloridot a tionil-klorid, szulfuril-klorid, foszgén, foszfor-pentaklorid, oxalil-klorid és a metán-szulfonil-klorid által alkotott csoportból választjuk ki, és amelyben az aktivált savklorid egy olyan Vilsmeier-reagens, amelynek képlete: $[XYC=N^+R_2]Cl^-$, ahol X hidrogénatom, aril- vagy alkil-csoport, ahol az aril- vagy alkil-csoport adott esetben halogénatommal, alkoxi-, tioalkoxi-, amido- vagy ciano-csoporttal szubsztituált; Y egy kilépő csoport, előnyösen Y jelentése halogénatom, heteroalkil-csoport vagy egy olyan csoport, amely helyettesíthető egy heteroatomos nukleofillel; és R egy hidrogénatom vagy alkilcsoport, amely adott esetben halogénatommal, alkoxi-, tioalkoxi-, amido- vagy ciano-csoporttal szubsztituált.

8. A 7. igénypont szerinti eljárás, amelyben X hidrogénatom, Y klóratom és R metilcsoport.

9. Az 1. igénypont szerinti eljárás, amelyben a TGS-6E szacharóz-6-benzoát-észter (TGS-6B), amely eljárás magában foglalja

(a) a szacharóz-6-benzoát-észternek N,N-dimetil-formamidban (DMF) való feloldását, amellyel egy szacharóz-6-benzoát-észtert tartalmazó oldatot kapunk;

(b) az (i) lépésbeli szacharóz-6-benzoát-észtert tartalmazó oldatnak egy klórozó-szerrel való összetevését, amellyel egy klórozó keveréket kapunk;

- (c) a klórozó reakcióból, DMF-HCl keverékként keletkező HCl legalább egy részének vákuum-desztillációval való eltávolítását, amellyel egy, TGS-6B-t és legalább egy alulklórozott szacharóz-6-benzoát-észtert tartalmazó keveréket kapunk;
- (d) a legalább egy alulklórozott szacharóz-6-benzoát-észternek egy klórozó lépésbe való visszavezetését, abból a célból, hogy a legalább egy alulklórozott szacharóz-6-benzoát-észtert továbbklórozzuk; és adott esetben
- (e) a (b)-(d) lépések "n" alkalommal való megismétlését, ahol $n \geq 1$.

10. A 9. igénypont szerinti eljárás, amely továbbá magában foglalja (f) a TGS-6B elválasztását a legalább egy alulklórozott szacharóz-6-benzoát-észterből.

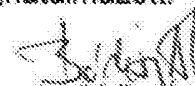
11. A 9. igénypont szerinti eljárás, amelyben a legalább egy alulklórozott szacharóz-6-benzoát-észtert, további klórozásra visszavezetjük az (a) lépésbe.

12. Az 1-11. igénypontok egyike szerinti eljárás, amelyben $n=2-8$.

13. Az 1-9. igénypontok egyike szerinti eljárás, amelyben a legalább egy alulklórozott szacharóz-6-észter diklór-galakto-szacharóz-6-benzoát.

14. Az 1-9. igénypontok egyike szerinti eljárás, amelyben a legalább egy alulklórozott szacharóz-6-észter monoklór-szacharóz-6-benzoát.

A meghatalmazott:



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