(19) DANMARK

(10) DK/EP 2646452 T3

(12) Oversættelse af europæisk patentskrift

Patent- og Varemærkestyrelsen

(51) Int.Cl.: *C 07 H 13/04 (2006.01)* *C 07 H 1/00 (2006.01)*

(45) Oversættelsen bekendtgjort den: **2016-06-20**

(80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2016-03-09**

(86) Europæisk ansøgning nr.: **12780983.8**

(86) Europæisk indleveringsdag: **2012-10-12**

(87) Den europæiske ansøgnings publiceringsdag: **2013-10-09**

(86) International ansøgning nr.: **US2012060068**

(87) Internationalt publikationsnr.: **WO2013056128**

(30) Prioritet: **2011-10-14 US 201161547356 P**

(84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**

(73) Patenthaver: **Lexington Pharmaceutical Laboratories, LLC, 14300 Clay Terrace Boulevard Suite 249, Carmel, Indiana 46032, USA**

(72) Opfinder: **ERICKSON, William, Randall, 4608 Buckingham Court, Carmel, Indiana 46033, USA**
FIELDS, Stephen, Craig, 10507 Silver Ridge Circle, Fishers, Indiana 46038, USA

(74) Fuldmægtig i Danmark: **JESPER LEVIN A/S, Strandvejen 656, 2930 Klampenborg, Danmark**

(54) Benævnelse: **CHLORERING AF CARBOHYDRATER OG CARBOHYDRATDERIVATER**

(56) Fremdragne publikationer:
EP-A1- 1 923 379
US-A- 4 980 463

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:

1. (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;
2. (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
3. (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 C_1-C_{18} aliphatic, C_6-C_{14} aryl C_1-C_{18} aliphatic or C_6-C_{14} aryl ester. Particularly suitable carboxylate esters include C_6-C_{10} 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, sulfuryl 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: $[XYC=N^+R_2]$ 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; 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, sulfuryl 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 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.

[0028] In any of the embodiments described above, the TGS-6E, e.g., sucralose-6-ester, is obtained in step (iii) 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.

[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 second 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:

1. (i) dissolving the sucrose-6-ester in N,N-dimethylformamide to obtain a solution comprising the sucrose-6-ester;
2. (ii) combining the solution comprising the sucrose-6-ester from step (i) with a chlorinating agent to obtain a chlorination mixture;
3. (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;
4. (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
5. (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 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.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- US4980463A [0001]
- WO2008052076A2 [0001]
- US20070100139A1 [0001]
- US20070207246A1 [0001]

- EP1923379A [0001]

Patentkrav

1. Fremgangsmåde til chlorering af en sucrose-6-ester til fremstilling af 4,1',6'-trichlor-4,1',6'-trideoxy-galactosucrose-6-*O*-ester (TGS-6E) med formlen M-OC(=O)R', hvor R' er en hydrofob gruppe, således at TGS-6E har en octanol/vand-fordelingskoefficient cLogP på 0,5 eller mere, og M er delen, der fuldstændiggør resten af TGS-6E, hvilken fremgangsmåde omfatter:

(i) at omsætte sucrose-6-esteren med et chloreringsmiddel i N,N-dimethylformamid (DMF) for at opnå en chloreringsreaktionsblanding, og at fjerne mindst en del af det HCl, som dannes ved chloreringsreaktionen, ved vakuumdestillation som en DMF-HCl-blanding for at opnå en reaktionsblanding, som omfatter nævnte TGS-6E og mindst én underchloreret sucrose-6-ester med formlen M'-OC(=O)R', hvor R' er en hydrofob gruppe, således at den underchlorerede sucrose-6-ester har en octanol/vand-fordelingskoefficient cLogP på 0,5 eller mere, og M' er delen, der fuldstændiggør resten af den underchlorerede sucrose-6-ester;

(ii) at føre den mindst ene underchlorerede sucrose-6-ester tilbage til et chloreringstrin og chlorere den mindst ene sucrose-6-ester yderligere for at opnå TGS-6E; og

(iii) eventuelt at gentage trin (i) og (ii) "n" gange, hvor n ≥ 1.

2. Fremgangsmåde ifølge krav 1, som yderligere omfatter:

(iv) at deaktivere mindst en del af reaktionsblandingen fra trin (i) for at opnå en deaktiveret reaktionsblanding og

(v) at isolere en produktblanding, som omfatter TGS-6E og mindst én underchloreret sucrose-6-ester, fra den deaktiverede reaktionsblanding.

3. Fremgangsmåde ifølge krav 1, hvor

(a) den mindst ene underchlorerede sucrose-6-ester føres tilbage til trin (i) til yderligere chlorering; eller

(b) hvor den yderligere chlorering af den mindst ene underchlorerede sucrose-6-ester finder sted i en beholder, som er adskilt fra den beholder, hvor trin (i) finder sted; eller

(c) hvor den yderligere chlorering af den mindst ene underchlorerede sucrose-6-ester finder sted i den beholder, hvor trin (i) finder sted.

4. Fremgangsmåde ifølge krav 2, hvor produktblandingen isoleres fra den deaktiverede reaktionsblanding ved ekstraktion med opløsningsmiddel i trin (v); og/eller hvor fremgangsmåden omfatter (vi) at separere den i trin (v) isolerede produktblanding i (a) en første fraktion, som omfatter TGS-6E, og (b) en anden fraktion, som omfatter den mindst ene underchlorerede sucrose-6-ester.

5. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 4, hvor TGS-6E, den mindst ene underchlorerede sucrose-6-ester eller en blanding deraf eventuelt kombineres med yderligere sucrose-6-ester og føres tilbage til et chloreringstrin eller til trin (i).

6. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 5, hvor R' er phenyl.

7. Fremgangsmåde ifølge et hvilket som helst af kravene 1 til 6, hvor chloreringsmidlet er et syrechlorid, et aktiveret syrechlorid eller bis(trichlormethyl)carbonat, fortrinsvis hvor syrechloridet er valgt fra gruppen bestående af thionylchlorid, sulfurylchlorid, phosgen, phosphorpentachlorid, oxalylchlorid og methansulfonylchlorid, og hvor det aktiverede syrechlorid er et Vilsmeier-reagens med formlen: $[XYC=N^{+}R_2]Cl^{-}$, hvor X er hydrogen, aryl eller alkyl, hvor arylgruppen eller alkylgruppen eventuelt er substitueret med halogen, alkoxy, thioalkoxy, amido eller cyano; Y er en leaving-gruppe, hvor Y fortrinsvis er halogen, heteroalkyl eller en gruppe, som kan fortrænges af en heteroatomholdig nukleofil; og R er hydrogen eller alkyl, som eventuelt er substitueret med halogen, alkoxy, thioalkoxy, amido eller cyano.

8. Fremgangsmåde ifølge krav 7, hvor X er hydrogen, Y er chlor, og R er methyl.

9. Fremgangsmåde ifølge krav 1, hvor TGS-6E er sucrose-6-benzoesyreester (TGS-6B), hvilken fremgangsmåde omfatter:

(a) at opløse sucrose-6-benzoesyreesteren i N,N-dimethylformamid (DMF) for at opnå en opløsning, som omfatter sucrose-6-benzoesyreesteren;

(b) at kombinere opløsningen fra trin (i), som omfatter sucrose-6-benzoesyreesteren, med et chloreringsmiddel for at opnå en chloreringsblanding;

(c) at fjerne mindst en del af det HCl, som dannes ved chloreringsreaktionen, ved vakuumdestillation som en DMF-HCl-blanding for at opnå en reaktionsblanding, som omfatter TGS-6B og mindst én underchloreret sucrose-6-benzoesyreester;

(d) at føre den mindst ene underchlorerede sucrose-6-benzoesyreester tilbage til et chloreringstrin for at chlorere den mindst ene underchlorerede sucrose-6-benzoesyreester yderligere; og eventuelt

(e) at gentage trin (b) til (d) "n" gange, hvor n ≥ 1.

10. Fremgangsmåde ifølge krav 9, som yderligere omfatter (f) at separere TGS-6B fra den mindst ene underchlorerede sucrose-6-benzoesyreester.

11. Fremgangsmåde ifølge krav 9, hvor den mindst ene underchlorerede sucrose-6-benzoesyreester føres tilbage til trin (a) til yderligere chlorering.

12. Fremgangsmåde ifølge krav 1 til 11, hvor n = 2 til 8.

13. Fremgangsmåde ifølge krav 1 eller 9, hvor den mindst ene underchlorerede sucrose-6-ester er dichlorgalactosucrose-6-benzoesyreester.

14. Fremgangsmåde ifølge krav 1 eller 9, hvor den mindst ene underchlorerede sucrose-6-ester er monochlorsucrose-6-benzoesyreester.