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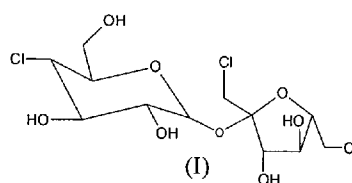
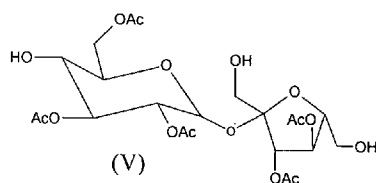
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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF 1, 6-DICHLORO-1, 6-DIDEOXY-BETA-D-FRUCTOFURANOSYL-4-CHLORO-4-DEOXY-ALPHA-GALACTOPYRANOSIDE



(57) Abstract: The present invention relates to an improved process for the preparation of 2, 3, 6, 3', 4'- Penta-O-acetylsucrose 6-PAS), formula (V) and sucralose, formula (I).

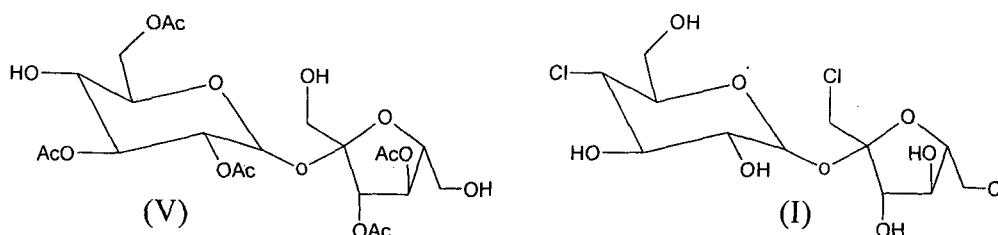
WO 2009/087677 A1

**AN IMPROVED PROCESS FOR THE PREPARATION OF
1, 6-DICHLORO-1, 6-DIDEOXY-BETA-D-FRUCTOFURANOSYL-4-
CHLORO-4-DEOXY-ALPHA-GALACTOPYRANOSIDE**

FIELD OF INVENTION

5 The present invention relates to an improved process for the preparation of 2, 3, 6, 3', 4'-Penta-O-acetylsucrose (6-PAS) and sucralose.

2, 3, 6, 3', 4'-Penta-O-acetylsucrose (6-PAS) is an important intermediate in the preparation of Sucralose. The structural formula of 6-PAS and Sucralose is represented by formula (V) and (I) respectively as given below.



BACKGROUND OF THE INVENTION

15 Sucralose is a potent sweetener having sweetness several hundred times that of sucrose. It is chemically known as 1,6-dichloro-1,6-dideoxy-β-D-fructofuranosyl-4-chloro-4-deoxy-α-galactopyranoside and having formula is C₁₂H₁₉Cl₃O₈ and molecular weight 397.64. Sucralose is used as sweetner in beverage, as coating tablet, chewing gum and other food products. It is marketed by McNeil under tradename Splenda®.

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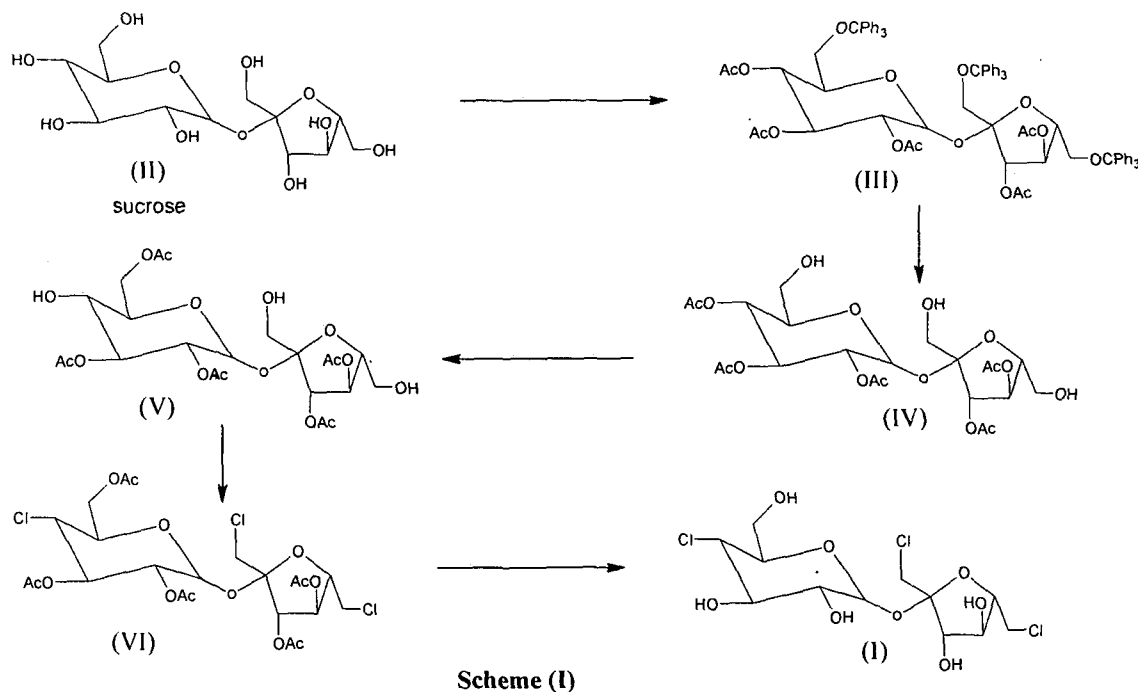
It is also chemically known as 4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose, (hereinafter referred to as "Sucralose") involves the substitution of chlorine atoms in the sucrose molecule in one of the five secondary hydroxyl positions and in two of the three primary hydroxyl positions. This particular selection of positions usually means that any synthetic route must involve the preparation of an intermediate sucrose derivative having the required positions available for chlorination while the other positions are blocked. In particular, the reactive 6-

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position must not be chlorinated, while the 4-position must be rendered available for chlorination.

A process for preparing Sucralose is set forth in U.S. Pat. No.4,362,869. This process converts sucrose through a number of steps into Sucralose. This process describes the sequential steps of (1) tritylation of sucrose to block the three primary alcohol groups; (2) acetylation of the five secondary alcohol groups as acetates; (3) detritylation of the three primary alcohol groups to deblock them; (4) acetyl migration from the 4-position to the 6-position; (5) chlorinating the desired alcohol groups at positions 4, 1', 6'; and (6) deblocking the remaining five alcohol groups by deacetylation using sodium methoxide in methanol thereby yielding Sucralose.

The schematic representation is as given below (Scheme I)



Scheme (I)

U.S. Patent No.4801700 discloses a process for preparation of Sucralose which comprise tritylation and acetylation, detritylation, acetyl migration and chlorination followed by

deacetylation. In this process, tritylation is done using trityl chloride in 3 portion in the presence of DMF and activated poly-2-vinylpyridine or N-methyl morpholine (NMM). Acetylation is done using acetic anhydride. Detritylation is carried out by passing HCl(g) in toluene wherein 2, 3, 4, 3', 4'-Penta-O-acetylsucrose (4-PAS) (IV) is precipitate out which is recovered by filtration. Acetyl migration is done using t-butylamine in ethylacetate and heptane to give 6-PAS which is inturn converted to sucralose by chlorination and deacetylation. In above process DMF and NMM used in tritylation step is removed under vacuum distillation. This also requires high temperature which may lead to degradation of the product. The removal of DMF at high temperature and degradation caused thereby makes the process less suitable at industrial scale.

US4362869A discloses a process for preparation of Sucralose wherein tritylation was carried out using trityl chloride in pyridine, acetylation using acetic anhydride, detritylation using acetic acid and conc. HCl solution, acetyl migration using acetic acid in methyl isobutyl ketone, chlorination using sulfuryl chloride and deacetylation was carried out using sodium methoxide to give Sucralose. The overall yield is 36% which is very low.

It is therefore, a need to develop a process which not only overcomes the abovementioned problems but also provides easy, simple and industrially applicable process.

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The present inventors have directed their research work towards developing a new process in which tritylation step is performed without the use of DMF. They developed an improved process in which they employed dimethylamino pyridine (DMAP) as catalyst and β -picoline as solvent in tritylation step. This change made the process not only easy at industrial scale but also environmentally friendly. They also found the yield of TRISPA (III) being improved which in turn increased the overall yield of sucralose.

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OBJECT OF THE INVENTION

A primary object of the present invention is to provide an improved process for the preparation of TRISPA (III) and 6-PAS (V).

- 5 Another object of the present invention is to provide an improved process for the preparation of Sucralose (I).

Another object of the present invention is to provide an improved process for the preparation of 6-PAS (V) in which TRISPA (III) is prepared by portion wise addition of trityl chloride in
10 the presence of catalyst DMAP and β -picoline as solvent.

Another object of the present invention is to provide an improved process for the preparation of Sucralose in which TRISPA (III) is prepared by portion wise addition of trityl chloride in the presence of catalyst DMAP and β -picoline as solvent.

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Yet another object of the present invention is to provide an improved process for the preparation of 6-PAS, which is simple, easy to handle and feasible at commercial scale.

SUMMARY OF THE INVENTION

20 In one aspect, present invention provides a process for the preparation of TRISPA (III) comprising steps of

- (i) tritylating sucrose using trityl chloride, dimethylamino pyridine (DMAP) as catalyst in β -picoline;
- (ii) acetylating using acetic anhydride to give TRISPA(III);

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In another aspect, present invention provides a process for the preparation of 6-PAS (V) comprising steps of

- (i) tritylating sucrose using trityl chloride, dimethylamino pyridine (DMAP) as catalyst in β -picoline;

- (ii) acetylating using acetic anhydride to give TRISPA(III);
- (iii) detritylating of TRISPA (III) using HCl(g) to give 4-PAS (IV);
- (iv) treating 4-PAS (IV) with t-butylamine to give 6-PAS (V).

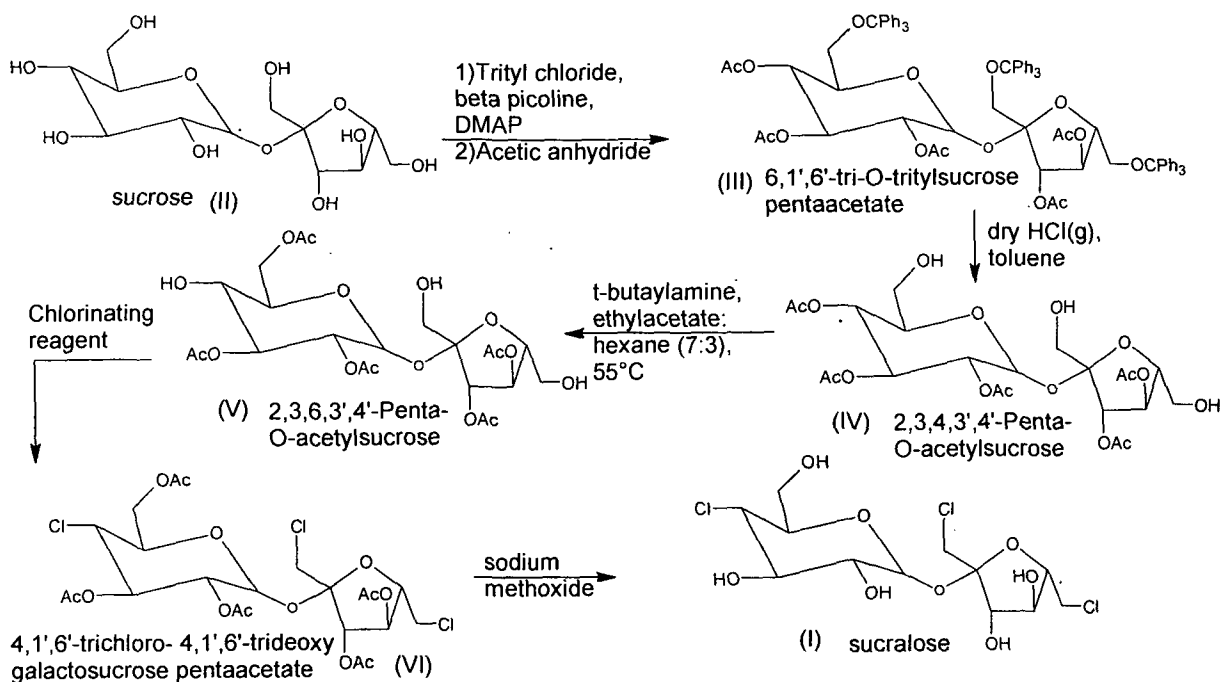
5 In yet another aspect, present invention provides a process for the preparation of Sucralose (I) comprising steps of

- (i) tritylating sucrose using trityl chloride, dimethylamino pyridine (DMAP) as catalyst in β -picoline;
- (ii) acetylating using acetic anhydride to give TRISPA(III);
- 10 (iii) detritylating of TRISPA (III) using HCl(g) to give 4-PAS (IV);
- (iv) treating 4-PAS (IV) with t-butylamine to give 6-PAS (V);
- (v) chlorinating 6-PAS using chlorinating reagent to give TOSPA;
- (vi) deacetylating 4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose pentaacetate (TOSPA) to give Sucralose.

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DETAILED DESCRIPTION OF THE INVENTION

The synthetic scheme is as shown below (Scheme I).



Scheme I

5 A process for the preparation of Sucralose (I) comprising steps of

- (a) preparing a mixture of sucrose, β -picoline and dimethylamino pyridine(DMAP); heating it to 50°C to 55°C , adding trityl chloride successively in three equal portions at the interval of approximately 1.5 hours, continuing stirring and heating for 8 to 10 hours, cooling the reaction mixture to 25°C to 30°C , adding acetic anhydride, heating the reaction mixture to 50°C to 55°C for 5 hours, cooling the reaction mixture to room temperature, adding toluene, water and conc. HCl and extracting, separating toluene layer and washing it with 20% sodium chloride solution;
- (b) cooling a solution of TRISPA in toluene obtained in step (a) to 0°C , passing dry HCl gas through the solution for 3 to 4hr, adding aqueous Sodium bicarbonate solution to the reaction mixture, separating aq. Layer and washing with toluene, adjusting pH of aq layer to 7 to 7.5 with sodium bicarbonate, extracting with dichloromethane, separating layers, adding sodium chloride to aq. Layer and extracting it with

dichloromethane, filtering combined dichloromethane layer through cartridge, evaporating the methylene chloride layer to obtain the solid 4-PAS;

- (c) adding a mixture of ethyl acetate: hexane (7:3) to 4-PAS, dehydrating the mixture at 65°C to 67°C, cooling the mixture to 50°C and adding t-butyl amine, heating the reaction mixture at 50°C to 55°C for 5 hr, cooling the reaction mixture to 30°C and stirring for 2 hr, filtering the solid and washing it with mixture of ethylacetate: hexane, drying the solid at 55°C to 65°C till constant weight to obtain 6-PAS;
- (d) chlorinating 6-PAS using chlorinating reagent to obtain TOPSA;
- (e) deacetylating TOPSA to obtain Sucralose.

The process of the present invention is described by the following examples, which are illustrative only and should not be construed so as to limit the scope of the invention in any manner.

Example-1

Preparation of 6, 1', 6'-Tri-O-tritylsucrose pentaacetate (TRISPA) (III)

A mixture of Sucrose (12kg) and β -picoline (36kg) was heated at 50°C to 55°C and catalytic amount of dimethylamino pyridine (DMAP) was added. Trityl chloride (31.2kg) was added in 3 portions at the interval of 1.5hr. The reaction mass was stirred for 8 to 10 hrs at 50°C to 55°C. After completion of the reaction, it was cooled to 30°C and acetic anhydride sufficient for acetylation was added to and heated to 50°C to 55°C for 5hr. The progress of the reaction was monitored on TLC. The reaction mixture was cooled to room temperature. Toluene (100L) and water (24L) was added to the reaction mixture and cooled to 10°C. Conc. HCl (33.5kg) was added at 10°C. β -picoline content was checked in organic layer. Aqueous layer was separated which is extracted with toluene. Combined toluene layer was washed twice with 20% w/w sodium chloride solution. The aqueous layer was transferred for recovery of β -picoline. The organic layer was dehydrated and taken as such for detritylation step.

Example-2**Preparation of Preparation of 2, 3, 4, 3', 4'-Penta-O-acetylsucrose (4-PAS)**

A solution of TRISPA in Toluene obtained in example-1 was cooled to 0°C under N₂ atmosphere. Dry HCl(g) was bubbled slowly through reaction at the same temperature for 3 to 4 hr. The progress of the reaction was monitored on TLC. Sodium carbonate (32kg) in Water (67L) was added to the reaction mixture at 10°C to 25°C during 30min and stirred for 20 min. Both layers were separated. Aq. layer was washed with toluene (10L). The pH of aq. layer was adjusted to 7 to 7.5 with sodium bicarbonate (6.5kg) at 15°C and stirred for 20min. Dichloromethane (20L) was added and extracted. Organic layer was separated. Sodium chloride (18kg) was added to the aqueous layer, stirred for 10 min and then extracted with Dichloromethane (8L). Organic layer was separated. Both organic layers were combined and filtered through cartridge. The clear organic layer was evaporated to dryness. A mixture of ethylacetate: hexane (7:3) (2L) was added to the residue and again distilled out to give 4-PAS

Example-3**Preparation of 2, 3, 6, 3', 4'-Penta-O-acetylsucrose (6-PAS)**

A mixture of ethyl acetate: hexane (7:3) (30L) was added to 4-PAS obtained in the example-2. The reaction mixture was heated to 66°C to 67°C and dehydrated. The reaction mixture was cooled to 50°C and t-Butyl amine (0.5L) was added. The reaction mixture was stirred for 5hr at 50°C to 55°C. After completion of conversion to 6-PAS, the reaction mixture was cooled to 30°C and stirred at the same temperature for 2hr. The solid was filtered, washed with mixture of ethylacetate: Hexane. The product was dried at 55°C to 65°C till constant weight obtained.

Example-4**Preparation of 4,1',6'-trichloro-4,1',6'-trideoxygalactosucrose pentaacetate (TOSPA)**

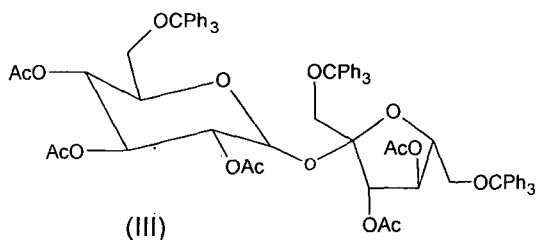
To slurry of 6-PAS (50 g) and triphenylphosphine sulphide (53.3 g) in xylene (150 ml) was added thionyl chloride (32.8 ml) and the mixture was heated at 115°C for 4.5 hr. Water (300 ml) was added and the biphasic mixture was vigorously stirred at 0°C for 1 hr. The crude

TOSPA was isolated by filtration and recrystallized from hot methanol to give solid product (31.8 g).

Example-5

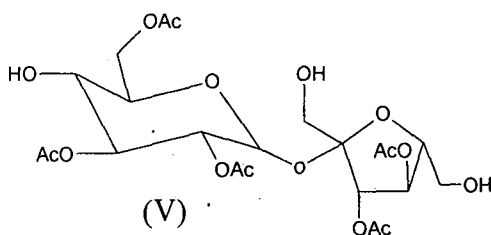
5 Preparation of Sucralose

TOSPA (50 g) is stirred at ambient with sodium methoxide (0.5 g) in methanol (125 ml) for 1.5 hours under vacuum. Heat is applied to maintain a temperature of 18°C to 20°C. TOSPA dissolves within 10 mins. The solution is neutralized by stirring with Amberlite IRC 50 (H⁺) resin (7.5 g) to, pH 7-7.5. The resin is removed by filtration and washed with methanol (25 ml), the filtrate and wash then being stirred with decolorizing charcoal (4 g) for 15 mins. The solution is clarified by filtrate and concentrated to a residue in vacuo. The sucralose is crystallized from ethyl acetate (100 ml), filtered, washed with ethyl acetate (25 ml) and dried in vacuo at 40°C for 12 hours to give solid (26 g)

CLAIMS**1. A process for the preparation of TRISPA (III)**

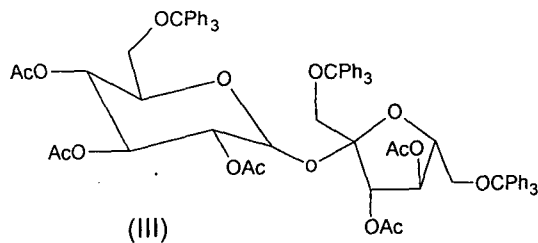
comprising steps of

- (i) titylating sucrose using trityl chloride, dimethylamino pyridine (DMAP) as catalyst in an organic Solvent;
- (ii) acetylating using acetic anhydride to give TRISPA(III);

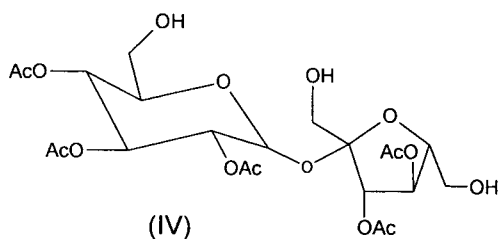
2. A process for the preparation of 6-PAS (V)

comprising steps of

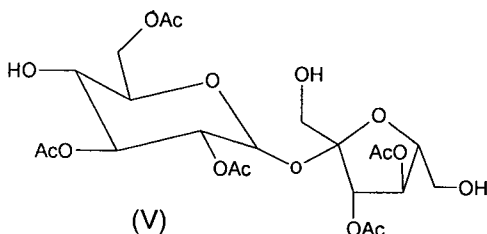
- (i) titylating sucrose using trityl chloride, dimethylamino pyridine (DMAP) as catalyst in an organic solvent;
- (ii) acetylating using acetic anhydride to give TRISPA(III);



- (iii) detritylating of TRISPA (III) using HCl(g) to give 4-PAS (IV);

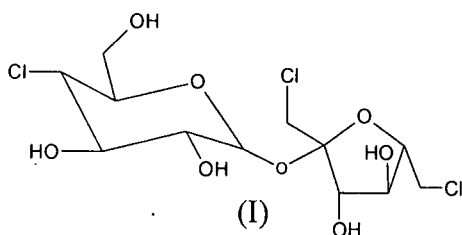


- (iv) treating 4-PAS (IV) with t-butylamine to give 6-PAS (V).



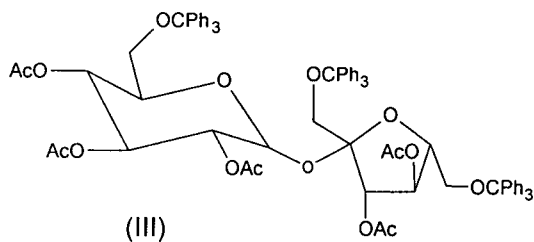
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3. A process for the preparation of Sucralose (I)



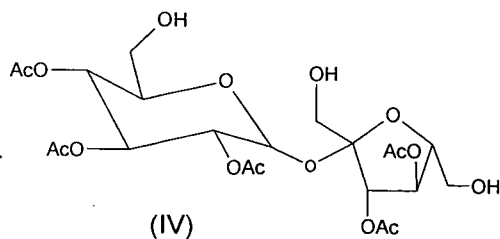
comprising steps of

- (i) tritylating sucrose using trityl chloride, dimethylamino pyridine (DMAP) as catalyst in β -picoline;
- (ii) acetylating using acetic anhydride to give TRISPA(III);

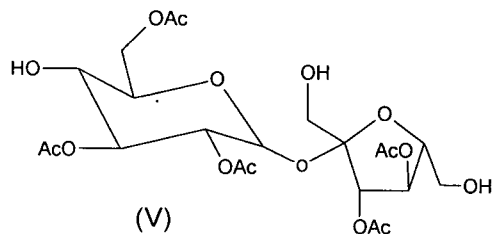


- (iii) detritylating of TRISPA (III) using HCl(g) to give 4-PAS (IV);

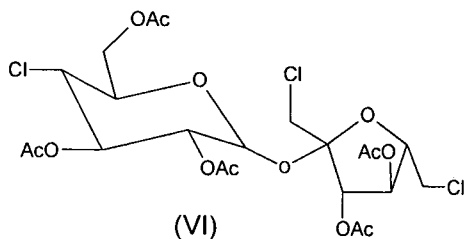
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(iv) treating 4-PAS (IV) with t-butylamine to give 6-PAS (V).



(vii) chlorinating 6-PAS using chlorinating reagent to give TOSPA (VI);



(viii) deacetylating 4,1',6'-trichloro-4,1',6'-trideoxysucrose pentaacetate (TOSPA) to give Sucralose (I).

4. The organic solvent as claimed in any of the preceding claims is selected from the group comprising β -picoline, pyridine and mixtures thereof.

5. A process for the preparation of Sucralose (I) comprising tritylating sucrose using trityl chloride, dimethylamino pyridine (DMAP) as catalyst in β -picoline.

6. A process for the preparation of Sucralose (I) comprising comprising,

(a) preparing a mixture of sucrose, β -picoline and dimethylamino pyridine(DMAP); heating it to 50°C to 55°C, adding trityl chloride successively in three equal portions at the interval of approximately 1.5 hours, continuing stirring and heating for 8 to 10 hours, cooling the reaction mixture to 25°C to 30°C, adding acetic anhydride, heating

the reaction mixture to 50°C to 55°C for 5 hours, cooling the reaction mixture to room temperature, adding toluene, water and conc. HCl and extracting, separating toluene layer and washing it with 20% sodium chloride solution;

5 (b) cooling a solution of TRISPA in toluene obtained in step (a) to 0°C, passing dry HCl gas through the solution for 3 to 4hr, adding aqueous Sodium bicarbonate solution to the reaction mixture, separating aq. Layer and washing with toluene, adjusting pH of aq. layer to 7 to 7.5 with sodium bicarbonate, extracting with dichloromethane, separating layers, adding sodium chloride to aq. Layer and extracting it with dichloromethane, filtering combined dichloromethane layer through cartridge,
10 evaporating the methylene chloride layer to obtain the solid 4-PAS;

(c) adding a mixture of ethyl acetate: hexane (7:3) to 4-PAS, dehydrating the mixture at 65°C to 67°C, cooling the mixture to 50°C and adding t-butyl amine, heating the reaction mixture at 50°C to 55°C for 5 hr, cooling the reaction mixture to 30°C and stirring for 2 hr, filtering the solid and washing it with mixture of ethylacetate:
15 hexane, drying the solid at 55°C to 65°C till constant weight to obtain 6-PAS;

(d) chlorinating 6-PAS using chlorinating reagent to obtain TOPSA;

(e) deacetylating TOPSA to obtain Sucralose.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2008/000853

A. CLASSIFICATION OF SUBJECT MATTER
 INV. C07H5/02 C07H15/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2007/072496 A (CAMLIN LTD [IN]; RAJADHYAKSHA MANGESH [IN]; SHIRWAIKER AJIT [IN] CAMLI) 28 June 2007 (2007-06-28) see in particular page 7	1-6
P,X	WO 2008/070043 A (TATE & LYLE TECHNOLOGY LTD [GB]; NOONAN ANNE [US]; SCHERRER STEVEN [US] 12 June 2008 (2008-06-12) see in particular page 6, lines 14-18 and page 13, line 37 to page 15, line 5	1-6
A	EP 0 223 421 A (MCNEILAB INC [US]) 27 May 1987 (1987-05-27) example XI	



Further documents are listed in the continuation of Box C.



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Date of the actual completion of the international search

16 June 2009

Date of mailing of the international search report

23/06/2009

Name and mailing address of the ISA/

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IN2008/000853

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