Process for the preparation of 1,6-dichloro-1,6-dideoxy-.beta.-D-fructofuranosyl-4-chloro-4-deoxy-.alpha.

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BACKGROUND OF THE INVENTION

This invention relates to a process for the preparation of 1,6-dichloro-1,6-dideoxy-.beta.-D-fructofuranosyl-4-chloro-4-deoxy-.alpha.-galactopyranoside. This compound is a potent sweetener, having a sweetness several hundred times that of sucrose. Its use as a sweetener and in sweetening compositions is disclosed in U.S. Pat. No. 4,435,440.

The preparation of 1,6-dichloro-1,6-dideoxy-.beta.-D-fructofuranosyl-4-chloro-4-deoxy-.alpha.-galactopyranoside or as it is sometimes referred to in the literature, 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-position must not be chlorinated, while the 4-position must be rendered available for chlorination.

One route proposed in the literature (Fairclough et al, Carbohydrate Research 40 (1975) 285-298) involves the formation of the 6,1',6'-tritrityl derivative of sucrose, peracetylation of the molecule and then detritylation with migration of the 4-acetyl radical to the 6-position, to give 2,3,6,3',4'-penta-O-acetylsucrose which has the correct hydroxy groups unprotected. Subsequent reaction with a chlorinating agent provides the 4,1',6'-trichlorogalactosucrose penta-acetate which in turn yields sucralose on removal of the acetyl groups. The chlorination proceeds with inversion of configuration at the 4-position. The 1' and 6'-positions freely rotate, but the 4-position cannot and the glucose ring is thus inverted at the 4-position yielding a galactose derivative so that the product is a galactosucrose.

Another route is set forth in U.S. Pat. No. 4,380,476 and comprises the steps of: (a) reacting sucrose with an acylating reagent under conditions to provide a mixture of acylated sucrose derivatives containing a major proportion of 6-monoacylated material; (b) optionally separating the 6-monoacylated sucrose derivative from other acylated derivatives before step (c); (c) reacting the monoacylated sucrose derivative with a chlorinating reagent capable of chlorinating at positions 1', 4 and 6' of a sucrose 6-acylate; and (d) deacylating and separating (in either order) the sucralose material formed.

A further 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 thereby yielding sucralose.

The invention disclosed in U.S. Pat. No. 4,362,869 is centered around the acetyl migration from the 4-position to the 6-position which is effected by treating a solution of 2,3,4,3',4'-penta-O-acetyl sucrose in an inert solvent with a weak acid at an elevated temperature. It was found that selection of specific reaction conditions for the acetyl migration gave considerably higher yields overall for separate detritylation and migration than the prior art which taught a one stage process for these steps. The weak acid utilized is preferably a carboxylic acid, especially an aliphatic carboxylic acid such as acetic acid. It is stated that any acid having an acid strength of the same order as acetic acid under the conditions used will suffice. The reaction temperature should be elevated above ambient temperature in order to provide an acceptable reaction time. A temperature of from about 80.degree. to 150.degree. C. is said to be suitable, preferably 100.degree. to 130.degree. C.

The inert solvent is said to be any solvent for penta-O-acetyl sucrose which remains liquid at the elevated temperature selected, e.g. a temperature in the range of 100.degree. to 140.degree. C. Ketonic solvents are particularly preferred, especially methyl isobutyl ketone, which refluxes at about 117.degree. C. A dilute solution of the acid in the solvent is said to be suitable, e.g. a solution of from 2 to 10% by weight, especially about 5%. This degree of dilution is suitable for reaction with the sucrose penta-acetate dissolved at a concentration of up to 30% by weight, e.g. about 20%. Ester solvents of sufficiently high boiling point are also useful, e.g. n-butyl acetate. Also of particular interest are aromatic hydrocarbons such as toluene or xylene.

When the reaction is completed, the reaction mixture is cooled an 2,3,6,3',4'-penta-O-acetylsucrose crystallizes. After an additional period of time at 0.degree. C., the crystalline product is filtered, washed and dried and then proceeds to the chlorination step. While an effective process, the above process involves the use of a carboxylic acid at high temperatures in the presence of free hydroxyl groups, conditions known to promote acylation.

SUMMARY OF THE INVENTION

The foregoing objects and other features and advantages of the present invention are achieved by an improved process for the preparation of sucralose. This process comprises the 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; (5) selective chlorination; and (6) deacetylation to deblock the remaining alcohol groups to yield sucralose.
Ph₃CCl + [Diagram]

\[ \text{(Step 1.2)} \]

1.1 S:CH₅N, 30 h, 30-35°C
1.2 6-12 h, rt
2.1 C:p-\(\text{MeC}_6\text{H}_4\text{SO}_3\text{H}\), S:MeOH, 2-4 h, 40-45°C
2.2 R:NaOH, S:H₂O, neutralized

3.1 R:Et-BnNH₂, S:DMF, 2.0-2.5 h, 20-25°C
4.1 R:Et-BnNH₂, S:SOCl₂, 1.5-4 h, 115°C
4.2 R:NaOH, S:H₂O, < 20°C, neutralized
5.1 R:NaOH, S:MeOH, 1.5-2 h, 40-45°C

NCTE: Reactants: 3, Reagents: 2, Catalysts: 1, Solvents: 5, Steps: 5, Stages: 0, Most stages in any one step: 2
Equal, Splenda Settle Lawsuit Over Ad Claims
By MARYCLAIRE DALE
The Associated Press
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PHILADELPHIA - The makers of Splenda and Equal on Friday settled a lawsuit over Splenda's disputed advertising slogan - "Made from sugar so it tastes like sugar."

The settlement came after the jury announced that it had reached a verdict.

Merisant Co., which makes Equal, accused Splenda of confusing consumers into thinking its product was healthier and more natural than other artificial sweeteners. Splenda's marketer, McNeil Nutritional, countered that it simply has a better product backed by superior advertising.

A McNeil spokeswoman in the courtroom said the amount of the settlement wouldn't be announced. The two sides planned to issue a joint statement later Friday.

Chicago-based Merisant was seeking more than $200 million from McNeil - at least $183 million for unfair profits since 2003 and compensation for at least $25 million in lost sales.

The active ingredient in Splenda starts as pure cane sugar but is chemically altered to create a compound that contains no calories, according to McNeil. The final product contains no sugar.

The one-month trial focused mostly on Splenda's advertising slogan, but it ended in a settlement after the jury said it had reached a verdict Friday afternoon.

Settlement talks began after jurors asked the judge for a calculator and a white board, an indication that they were computing damages to be awarded to Merisant. Lawyers rushed to the courtroom to try to delay the jury's announcement and then huddled in a courthouse meeting room.

McNeil's own consultants said its slogan confused potential customers, some of whom thought that Splenda was sugar without the calories, Merisant's attorneys said. McNeil rejected a plan to add the phrase "does not contain sugar" to the front of Splenda's yellow box, which might have cleared up the confusion, Merisant said.

Because the manufacturing of Splenda begins with sugar, McNeil can accurately claim that Splenda is "made from" sugar, according to its attorneys.

Splenda is used in more than 4,000 food and drink products and is included in recipes at numerous chain restaurants.

It had 60 percent of the consumer artificial sweetener market last year, according to the research firm Information Resources Inc. Equal, which comes in blue packets and is made with aspartame, and Sweet'N Low, in pink packets and made with saccharin, each held about 14 percent of the consumer market.