

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property
Organization

International Bureau

(43) International Publication Date
05 March 2020 (05.03.2020)



(10) International Publication Number
WO 2020/043639 A1

(51) International Patent Classification:

C07D 307/20 (2006.01)

(21) International Application Number:

PCT/EP2019/072661

(22) International Filing Date:

26 August 2019 (26.08.2019)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

PCT/CN2018/102509

27 August 2018 (27.08.2018)	CN
62/736,060	25 September 2018 (25.09.2018) US
18196446.1	25 September 2018 (25.09.2018) EP
19151606.1	14 January 2019 (14.01.2019) EP
19176534.6	24 May 2019 (24.05.2019) EP
19000293.1	14 June 2019 (14.06.2019) EP
19187318.1	19 July 2019 (19.07.2019) EP
19187974.1	24 July 2019 (24.07.2019) EP

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))
- as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
- of inventorship (Rule 4.17(iv))

Published:

- with international search report (Art. 21(3))

(71) Applicants: **LONZA GUANGZHOU NANSHA LTD.**

[CN/CN]; 68, Huangge Dadaobei, Nansha District, Guangzhou, 511455 (CN). **LONZA LTD** [CH/CH]; Lonzastrasse, 3930 Visp (CH).

(72) Inventors: **WEI, Jieping**; Xinghe Shenshi, Room

No.:4-1-1104, Jinsha road, Guangzhou District, Nansha District 511457 (CN). **YANG, Yanling**; Media Village North, Room No.:12-803 xingya 2 road, Asian Games Town, Guangzhou, Panyu District 511447 (CN). **SHAN, Daniel**; Dalongjie Yayundadao 498, Guangzhou, Panyu District 511450 (CN). **ZHU, Reta**; 3rd Floor, No. 7 Qian-Fu Street, QiFu Road, Guangzhou, Panyu District 511496 (CN). **HANSELMANN, Paul**; Holzachra 25, 3902 Brig-Glis (CH). **SCHERER, Dieter**; Im Tschambol 18, 4242 Laufen (CH).

(74) Agent: **GREINER, Elisabeth**; df-mp Dörries Frank-Mol-

nia & Pohlman, Patentanwälte Rechtsanwälte PartG mbB, Theatinerstraße 16, 80333 Munich (DE).

(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(54) Title: METHOD FOR PREPARATION OF 1,4-SORBITAN

(57) Abstract: The invention discloses a method for preparation of 1,4-sorbitan by dehydration of D-sorbitol, wherein one equivalent of water is removed and a cyclization occurs, followed by a treatment with ethanol and isopropanol.



METHOD FOR PREPARATION OF 1,4-SORBITAN

The invention discloses a method for preparation of 1,4-sorbitan by dehydration of D-sorbitol, wherein one equivalent of water is removed and a cyclization occurs, followed by a treatment with ethanol and isopropanol.

5

1,4-Sorbitan is used for the production of pharmaceuticals, such as certain prostaglandin analogues, and for the production of excipients used in formulation of pharmaceuticals, such as Polysorbate 80.

10 S. Stolzberg, J. Am. Chem.Soc., 1946, 68, 919-921, discloses a method for preparation of 1,4-sorbitan by a dehydration of 100 g sorbitol in the presence of concentrated sulfuric acid and water at ca. 140°C for 30 min, the method has a recrystallization step from isopropanol as a last step, reported yield is 33 g; the calculated molar yield is 36.6%.

15 US 2002/0002284 A1 discloses a method for preparation of 1,4-sorbitan by dehydration of 4 kg D-sorbitol in the presence of sulfuric acid and water at 104°C for ca. 52 h, the method has a recrystallization step from ethanol as a last step, reported yield is 1.693 kg, the calculated molar yield is 47.0%. Besides sulfuric acid, also Na₂CO₃, isopropanol, Na₂SO₄, ethanol, activated charcoal and toluene are used in considerable amounts. The method comprises 3
20 filtration steps besides the dehydration step and the recrystallization step.

CN 101948451 A discloses a method for preparation of high-purity 1,4-sorbitan, which is characterized by taking sorbitol as a raw material through two times of dehydration and three times of crystallization. Already after the second dehydration, a base is added to the reaction
25 mixture for neutralization, then the reaction mixture is filtered to remove an acid catalyst used in the second dehydration reaction, the a decolourization is done by addition of activated carbon, which again necessitates a filtration for removing the activated carbon. The crystallization is done with methanol, after each crystallization step a filtration is done. The content of 1,4-sorbitan is 73.7% after the decolourization, 87% after the first, 94% after the
30 second and 99.2% after the third crystallization. The yield after the decolourization was 70%, the yield after the three crystallization was 19%, so the overall yield was 13%.

CN 106167476 A discloses in [0028] S1 a preparation of 1,4-Sorbitan from a melt of sorbitol with a catalyst which is composed of tetrabutylammonium bromide and p-toluene sulfonic

acid. No yield and also no analytical data is given of any amounts of sorbitol or of isosorbide in the product.

A reworking of this example as disclosed herein under "Comparative Example 1" showed inter alia, that the product is a sticky liquid, the yield is very low with 9.6% and there are still
5 considerable amounts of D-sorbitol (ca. 28%) and of isosorbide (2.5%) in the product.

US 2016/0130277 A1 (US'277) discloses in Example 1 the dehydration of Sorbitol to provide 1,4-sorbitan. The reported yield of 35% is significantly lower than the yield of 52.6 % of inventive Example 1.

10 Reworking of this Example 1 of US'277, as reported herein under Comparative Example 2, was not possible. In particular the crystallization of the reported residue after the reaction from cold methanol was not possible even though the procedure as reported in Example 1 US'277 up to this point was follow literally. The analysis of the this residue shows a significantly higher relative content of sorbitol and a significantly lower relative content of
15 1,4 sorbitan compared to the analysis of the equivalent intermediate in the clear solution in ethanol in the inventive example 1. This difference in the relative amounts of 1,4 sorbitan and sorbitol correlates well with the reported significantly lower yield of Example 1 of US'277. The reaction in Example 1 of US'277 is done under a pressure of 50 bar.

20 Any use of a compound for or in pharmaceutical applications requires a defined purity and usually also a high purity.

There was a need for a method for preparation 1,4-sorbitan with high yield, high purity, low content of isosorbide or D-sorbitol; the method should be as economic as possible, such as
25 with a low number of steps such as filtration or with a low number of different chemicals used, also the method should be suited to be done "in one pot", meaning that only one reactor can be used.

Unexpectedly, a method was found which gives high yield, high purity, low content of
30 isosorbide, low content D-sorbitol; the method is economic, has a low number of steps such as filtration and uses a low number of different chemicals. The method can be done in one reactor. The method provides 1,4-sorbitan with considerable higher yields and purity compared to the example [0028] S1 of CN 106167476 A.

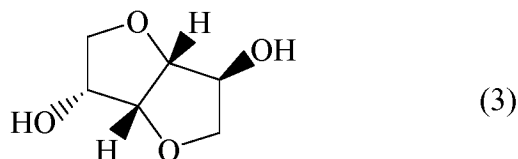
Abbreviations:

DMSO dimethyl sulfoxide

equiv equivalent

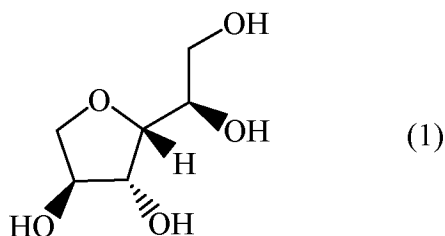
Isosorbide compound of formula (3), MW 146,1 g/mol, CAS 652-67-5

5



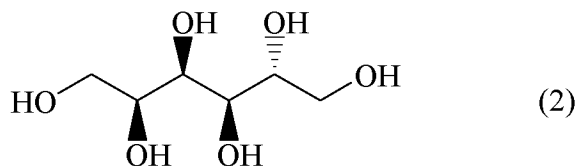
1,4-Sorbitan compound of formula (1), MW 164,2 g/mol, CAS 27299-12-3

10



D-Sorbitol compound of formula (2), MW 182.2 g/mol, CAS 50-70-4

15



MW molecular weight

TBAB Tetrabutylammonium bromide

% percent are percent by weight (wt%), if not stated otherwise

- 20 Subject of the invention is a method for preparation of 1,4-sorbitan with four consecutive steps STEP1, STEP2, STEP3 and STEP4, wherein
- in STEP1 D-sorbitol is dehydrated in a dehydration reaction DEHYDREAC in the presence of p-toluenesulfonic acid and tetrabutylammonium bromide, STEP1 provides a mixture MIX1;
- 25 in STEP2 ethanol is mixed with MIX1, STEP2 provides a mixture MIX2;
- in STEP3 isopropanol is mixed with MIX2, STEP3 provides a mixture MIX3;

in STEP4 1,4-sorbitan is isolated from MIX3.

Preferably, the p-toluene sulfonic acid is used in form of p-toluenesulfonic acid monohydrate;
so in any embodiment where p-toluene sulfonic acid is mentioned, the preferred
5 embodiment is p-toluenesulfonic acid monohydrate.

Preferably, no solvent is present in or used for DEHYDREAC.

Preferably, no water is charged for DEHYDREAC.

Preferably, DEHYDREAC is done neat, that is only the three components D-sorbitol, p-
10 toluenesulfonic acid and tetrabutylammonium bromide are used for and are charged for
DEHYDREAC.

Preferably, the molar equivalent of p-toluenesulfonic acid in DEHYDREAC acid is from 0.2
to 1.6%, more preferably from 0.4 to 1.4%, even more preferably from 0.6 to 1.2%,
15 especially from 0.6 to 1.0%, of the molar equivalents of D-sorbitol.

Preferably, the molar equivalent of tetrabutylammonium bromide in DEHYDREAC acid is
from 1.0 to 3.6%, more preferably from 1.2 to 3.2%, even more preferably from 1.4 to
2.8%, especially from 1.6 to 2.4%, more especially from 1.6 to 2.0%, of the molar
equivalents of D-sorbitol.

20 Preferably, the weight of ethanol mixed in STEP2 is from 0.2 to 5 fold, more preferably from
0.2 to 2 fold, even more preferably from 0.2 to 1 fold, especially from 0.2 to 0.8 fold,
more especially from 0.2 to 0.6 fold, even more especially from 0.3 to 0.5 fold, of the
weight of D-sorbitol.

Preferably, the weight of isopropanol mixed in STEP2 is from 0.2 to 5 fold, more preferably
25 from 0.2 to 2 fold, even more preferably from 0.2 to 1 fold, especially from 0.2 to 0.8
fold, more especially from 0.2 to 0.6 fold, even more especially from 0.3 to 0.5 fold, of
the weight of D-sorbitol.

Preferably, DEHYDREAC is done at a temperature TEMP1, TEMP1 is from 95 to 130 °C,
30 more preferably from 95 to 120°C, even more preferably from 100 to 115°C, especially
from 105 to 115°C, in particular 110°C.

Preferably, the reaction time TIME1-1 of DEHYDREAC is from 3 to 12 h, more preferably
from 4 to 12 h, even more preferably from 5 to 10 h, especially from 5 to 8 h, more
especially from 5 to 7 h, in particular 6 h.

In another embodiment, TIME1-1 is preferably from 6 to 10 h, more preferably from 7 to 9 h. Preferably, DEHYDREAC is done at a pressure PRESS1 of 500 mbar or below, more preferably of 250 mbar or below, even more preferably of 100 mbar or below, especially of 50 mbar or below, more especially of 25 mbar or below, even more especially of 15 mbar or below, in particular of 10 mbar or below.

The lower limit of the pressure may be anything which is technically feasible. Examples for a lower limit of the pressure may be 0.1 mbar, or 0.5 mbar, or 1 mbar, or 2 mbar.

In another embodiment, DEHYDREAC is done at PRESS1 of from 0.001 to 500 mbar, preferably of from 0.001 to 250 mbar, more preferably of from 0.001 to 100 mbar, especially of from 0.001 to 50 mbar, more especially of from 0.01 to 25 mbar, even more especially of from 0.1 to 15 mbar, in particular of from 1 to 15 mbar, more in particular of from 1 to 12.5 mbar, even more in particular 4 to 6 mbar.

Preferably, STEP2, STEP3 and STEP4 are done at atmospheric pressure.

Water is formed by DEHYDREAC as the reaction is a dehydration, which removes 1 equiv of water. When the p-toluene sulfonic acid is used in form of p-toluenesulfonic acid monohydrate, it can also be a source of water during DEHYDREAC.

Preferably, water is removed during DEHYDREAC.

Preferably, STEP2 is done at a temperature TEMP2 of from 60 to 90°C, more preferably of from 60 to 85°C, even more preferably of from 65 to 80°C, in particular of from 70 to 75°C.

Preferably, STEP1 comprises a cooling COOL1 after DEHYDREAC, where MIX1 is cooled from TEMP1 to TEMP2.

Preferably, COOL1 is done in a time TIME1-2, TIME1-2 is from 10 min to 10 h, more preferably from 15 min to 5 h, even more preferably from 15 min to 2 h, especially from 20 min to 1 h, in particular in 30 min.

Preferably, if DEHYDREAC has been done at PRESS1, then the pressure can be brought back from PRESS1 to atmospheric pressure after DEHYDREAC. If STEP1 comprises COOL1 and DEHYDREAC has been done at PRESS1, then the pressure can be brought back from PRESS1 to atmospheric pressure before, during or after COOL1.

Preferably, after the mixing of ethanol, STEP2 comprises a stirring STIRR2 of MIX2 for a time TIME2-1, TIME2-1 is from 30 min to 10 h, more preferably of from 1 to 8 h, even more preferably of from 1 to 6 h, especially from 1 to 4 h, more especially from 1.5 to 3 h, in particular 2 h.

5 Preferably, STIRR2 is done at TEMP2.

Preferably, STEP3 is done at a temperature TEMP3-1 of from 10 to 30°C, more preferably of from 15 to 25°C, even more preferably of from 17.5 to 22.5°C, in particular 20°C.

10 Preferably STEP2 comprises a cooling COOL2, where MIX2 is cooled from TEMP1 or TEMP2 to TEMP3-1.

Preferably, COOL2 is done after STIRR2.

Preferably, COOL2 is done from TEMP2 to TEMP3-1.

Preferably, STEP2 comprises STIRR2 and COOL2, and COOL2 is done after STIRR2.

15 Preferably, COOL2 is done in a time TIME2-2, TIME2-2 is from 1 to 10 h, more preferably from 1 to 8 h, even more preferably from 1 to 6 h, especially from 1 to 4 h, more especially from 2 to 4 h, in particular 3 h.

Preferably, after the mixing of isopropanol, STEP3 comprises a cooling COOL3 of MIX3 to a temperature TEMP3-2 of from -5 to 5°C, more preferably of from -2.5 to 2.5°C, even more preferably of from -1 to 2°C, in particular 0°C.

20 Preferably, COOL3 is done in a time TIME3-1, TIME3-1 is from 30 min to 10 h, more preferably of from 30 min to 8 h, even more preferably of from 30 min to 6 h, especially from 30 min to 4 h, more especially from 30 min to 2 h, in particular 1 h.

Preferably, STEP3 comprises a stirring STIRR3 of MIX3, STIRR3 is done for a time TIME3-2, TIME3-2 is from 1 to 12 h, more preferably from 1 to 10 h, even more preferably

25 from 2 to 8 h, especially from 2 to 6 h, more especially from 3 to 5 h, in particular 4 h.

Preferably, STIRR3 is done after COOL3.

Preferably, STIRR3 is done at TEMP3-2.

More preferably, STIRR3 is done after COOL3 and STIRR3 is done at TEMP3-2.

30 The isolation in STEP4 of 1,4-sorbitan from MIX3 can be done by any means known to the skilled person, such as evaporation of any liquids in MIX3, filtration, centrifugation, drying, or a combination thereof, preferably the isolation is done by filtration or centrifugation of MIX3, more preferably by filtration, preferably followed by drying of the provided isolated solid product.

Preferably, 1,4-sorbitan is isolated in STEP4 from MIX3 by filtration providing a presscake, preferably followed by washing the presscake with isopropanol, preferably followed by drying of the washed presscake, preferably the drying is done at a temperature of from 30 to 70°C, more preferably of from 40 to 60°C, in particular 50°C.

5

In one embodiment,

STEP1 comprises consecutively DEHYDREAC and COOL1;

STEP2 comprises after the mixing of ethanol consecutively STIRR2 and COOL2;

STEP3 comprises after the mixing of isopropanol consecutively COOL3 and STIRR3;

10 STEP4 comprises an isolation of 1,4-sorbitan by a filtration of MIX3, preferably followed by washing and drying.

Preferably, in STEP2 ethanol is charged to MIX1 providing MIX2.

Preferably, in STEP3 isopropanol is charged to MIX2 providing MIX3.

15

Preferably, STEP1 and STEP2 are done consecutively without isolation, such as by filtration, of the 1,4-sorbitan between STEP1 and STEP2.

Preferably, STEP2 and STEP3 are done consecutively without isolation, such as by filtration, of the 1,4-sorbitan between STEP2 and STEP3.

20 More preferably, STEP1, STEP2 and STEP3 are done consecutively without isolation, such as by filtration, of the 1,4-sorbitan between STEP1 and STEP2 and without isolation, such as by filtration, of the 1,4-sorbitan between STEP2 and STEP3.

Preferably, STEP1, STEP2 and STEP3 are done consecutively in one and the same reactor.

25

There is no need to use camphorsulfonic acid, sulfuric acid, Na₂CO₃, Na₂SO₄, activated charcoal or toluene in the method of instant invention.

Preferably, no sulfuric acid is used in STEP1;

more preferably, no sulfuric acid is used in STEP1, STEP2, STEP3 or STEP4.

30 Preferably, no camphorsulfonic acid is used in STEP1;

more preferably, no camphorsulfonic acid is used in STEP1, STEP2, STEP3 or STEP4.

Preferably, no Na₂CO₃, Na₂SO₄, activated charcoal or toluene are used in STEP2 or STEP3;

more preferably no Na₂CO₃, Na₂SO₄, activated charcoal or toluene are used in STEP2, STEP3 or STEP4;

even more preferably no Na_2CO_3 , Na_2SO_4 , activated charcoal or toluene are used in STEP1, STEP2, STEP3 or STEP4.

Preferably, the method of instant invention does not use azeotropic removal of water, more preferably azeotropic removal of water facilitated by the presence of toluene during the azeotropic removal of water for providing the azeotrope.

Preferably, after the isolation of the product in STEP4 there is no recrystallization, for example from EtOH.

More preferably, none of the steps STEP1, STEP2, STEP3 and STEP4 comprise a recrystallization after an isolation, for example from EtOH.

Examples

Materials

The materials were used in the following qualities, if not otherwise stated:

5	D-Sorbitol	98 wt%
	TsOH-H ₂ O	99 wt%
	TBAB	98 wt%
	Ethanol	99 wt%
	Isopropanol	99 wt%

10

Methods:

(1) GC

Instrument parameters

Column DB-1 HT (30 m * 0.25 mm * 0.1 µm) Agilent Technologies, Santa Clara, USA

15 Temperature program:

Initial; time 100 °C; 0 min

Rate1; Final 1; Time 1 8°C/min; 350°C; keep 10min

Run Time 41.25 min

Equilibration Time 0.5min

20 Mode Cons. flow

Carrier gas H₂

Flow 1.5 ml/min

Split ratio 10:1

Inlet Temperature 350 °C

25 Injection Volume 1 microliter

Detector temperature 350°C

Sample preparation

Sample stock solution

Add 2 g sample to 5 ml pyridine and 10 ml acetic anhydride in a screw-cap bottle (25 mL)

30 and heat up to 120°C for 2 hours under stirring.

Sample solution

0.5 ml of Sample stock solution is added into an autosampler vial with 1 ml of dichloromethane and mixed

1,4-Sorbitan is detected at ca. 12.3 min.

(2) ¹H NMR

Solvent: DMSO-d₆

5 to 10 mg of sample were dissolved in 0.6 ml of DMSO-d₆ and mixed.

5

(3) ¹³C NMR

Solvent: DMSO-d₆

20 to 50 mg of sample were dissolved in 0.6 ml of DMSO-d₆ and mixed well.

10 (4) Optical rotation method**Instrument parameters**

Instrument	MCP 300 of Anton Paar GmbH, Graz, Austria
Wavelength	589 nm
Cell	100.00 mm
15 Temperature	20.0 °C
Response	2 s
Measure	N=5
Delay	10 s
Stable Temperature	±0.3°C

20 Sample preparation**Blank**

Pure water

Sample solution

300±3 mg of 1,4-Sorbitan was added into a 100 ml volumetric flask, then dissolved with
25 water and diluted to volume.

Example 1

D-sorbitol (300 g, 1.647mol, 1 equiv) was charged into a 1.5 L reactor. p-Toluenesulfonic acid monohydrate (2.665 g, 0.014 mol, 0.0085 (0.85%) equiv) was charged, followed by
30 charging of TBAB (9.6 g, 0.03 mol, 0.0182 (1.81 %) equiv). Vacuum of reactor 4 to 6 mbar was applied. Then the mixture was heated to 110°C (the mixture melted at around 90°C) and stirred at 110°C for 6 hours. The mixture was cooled to 70 to 75 °C in 30 min. Ethanol (150 mL) was charged. The resulting mixture was stirred at 70 to 75 °C for 2 hours and formed a clear solution. Then the solution was cooled to 20 °C in 3 hours. A yellow suspension was

formed. Isopropanol (150 mL) was charged. The mixture was cooled to 0 °C in 1 hour. The mixture was slurry at 0 °C for 4 hours. The mixture was filtered, and the cake was washed with isopropanol (150 mL). The cake was dried at 50 °C for 16 hours under vacuum to provide 142.2 g of product as white solid.

5 Yield 52.6%

¹H NMR and ¹³C NMR confirmed the structure.

GC area-%:

	1,4-Sorbitan	97%
10	Isosorbide	0.14%
	D-Sorbitol	0.12%

Specific Rotation: -22.26°, c=3.1 (water)

Comparative Example 1

15 [0028] S1 of Example 1 of CN 106167476 A was repeated literally word by word. The translation of the example from Chinese into English was provided by a Chinese patent attorney:

[0028] S1 Adding solid sorbitol powder into the reactor; raising the temperature to 90°C;
20 stirring the powder in the reactor until it turns to a molten state; adding catalyst I, wherein the catalyst I is added in an amount of 4% by weight of the solid sorbitol powder, and the catalyst I is composed of tetrabutylammonium bromide and p-toluene sulfonic acid in a weight ratio of 3:2; and stirring the mixture uniformly; dehydrating the mixture for 2 hours at a
temperature of 100°C under the vacuum degree from 0.006 MPa; filtering, and treating the
25 dehydrated mixture for 50 minutes by adding activated carbon when the temperature is lowered to 35°C, wherein the activated carbon is added in an amount of 0.3% of the total weight of the solid sorbitol powder and the catalyst I, and the activated carbon has an average particle diameter of 48µm; and filtering, concentrating, and drying to obtain 1, 4-Sorbitan.

30 The following results were obtained in this Comparative Example 1:

The product was a colorless and sticky liquid.

Yield: 9.6%

GC area-% of

- 1,4-Sorbitan: 56.9%

- Isosorbide: 2.5%
- D-Sorbitol: 28.7%

Observation:

- 5 From the beginning, that is from the melting of the solid sorbitol powder, until the end, that is the obtained product, the physical form is a sticky liquid. No solid product is obtained in any stage of the process.

Comparative Example 2

- 10 Example 1 of US 2016/0130277 A1 in [0048] was repeated literally in the following way:
D-Sorbitol (20 g, 110 mmol) and 0.1% (mol/mol) camphorsulfonic acid are added in a 150 ml stainless steel autoclave. The reactor is sealed hermetically, purged with hydrogen three times and then hydrogen was introduced up to a pressure of 50 bar. The system is then heated to 140° C. and shaken with a mechanical shaker for 15
15 *hours. After cooling to room temperature, the hydrogen pressure was released and the white foam was diluted in ethanol (200 ml) in order to obtain a yellow homogeneous mixture. Solvent is evaporated under reduced pressure.*

- According to the description of this Example 1 the obtained residue should now be
20 crystallized from cold methanol followed by vacuum filtration.

This crystallization was tried several times with different amounts of methanol and with different temperatures but surprisingly it was not possible to do such crystallization. Even when cooling the solution in methanol to 0 °C no crystallization occurred.

25

GC analysis revealed a GC area-% of:

1,4 sorbitan	54.90 %
sorbitol	32.42 %

- 30 This residue of Example 1 of US'277 can be compared with the product obtained in Example 1 of this invention at the following point in the procedure of Example 1 of this invention:

After having stirred at 110°C for 6 hours, the mixture was cooled to 70 to 75 °C in 30 min. Ethanol (150 mL) was charged. The resulting mixture was stirred at 70 to 75 °C for 2 hours and formed a clear solution.

GC analysis of this clear solution in EtOH revealed a GC area-% of:

1,4 sorbitan	74.97 %
sorbitol	2.87 %

5 It is assume that the much higher content of sorbitol in the residue that was obtained in this reworking of Example 1 of US'277 in Comparative Example 2 prevented crystallization. of said residue No reason for the non-working of the crystallization can be found in the way how the reworking was carried out, the procedure given in Example 1 of US'277 was followed literally until said residue.

10

In any case the relative content of the desired 1,4 sorbitan is significantly lower and the relative content of undesired sorbitol is significantly higher in this residue of Example 1 of US'277 when compared with the equivalent reaction mixture in form of the clear solution in EtOH of the inventive Example 1.

15 This difference in the relative amounts of these two substances correlates with the significantly lower yield of 35 % reported in Example 1 of US'277, compared to the yield of 52.6 % of inventive Example 1.

This difference in the yields shows that the process of the invention is an improved procedure compared with the process of Example 1 of US'277.

20

Claims

1. A method for preparation of 1,4-sorbitan with four consecutive steps STEP1, STEP2, STEP3 and STEP4, wherein
 - 5 in STEP1 D-sorbitol is dehydrated in a dehydration reaction DEHYDREAC in the presence of p-toluenesulfonic acid and tetrabutylammonium bromide, the reaction time TIME1-1 of DEHYDREAC is from 3 to 12 h; DEHYDREAC is done at a temperature TEMP1, TEMP1 is from 95 to 130 °C, DEHYDREAC is done at a pressure PRESS1 of 500 mbar or below,
 - 10 STEP1 provides a mixture MIX1;
 - in STEP2 ethanol is mixed with MIX1, STEP2 provides a mixture MIX2;
 - in STEP3 isopropanol is mixed with MIX2, STEP3 provides a mixture MIX3;
 - in STEP4 1,4-sorbitan is isolated from MIX3.
- 15 2. The method according to claim 1, wherein the p-toluene sulfonic acid is used in form of p-toluenesulfonic acid monohydrate.
3. The method according to claim 1 or 2, wherein DEHYDREAC is done neat, that is only the three components D-sorbitol, p-toluenesulfonic
 - 20 acid and tetrabutylammonium bromide are used for and are charged for DEHYDREAC.
4. The method according to one or more of claims 1 to 3, wherein DEHYDREAC is done at a temperature TEMP1, TEMP1 is from 95 to 120°C.
- 25 5. The method according to one or more of claims 1 to 4, wherein the reaction time TIME1-1 of DEHYDREAC is from 4 to 12 h.
6. The method according to one or more of claims 1 to 5, wherein DEHYDREAC is done at a pressure PRESS1 of 250 mbar or below.
 - 30
7. The method according to one or more of claims 1 to 6, wherein water is removed during DEHYDREAC.
8. The method according to one or more of claims 1 to 7, wherein

STEP2 is done at a temperature TEMP2 of from 60 to 90°C.

9. The method according to one or more of claims 1 to 8, wherein STEP3 is done at a temperature TEMP3-1 of from 10 to 30°C.

5

10. The method according to one or more of claims 1 to 9, wherein after the mixing of isopropanol, STEP3 comprises a cooling COOL3 of MIX3 to a temperature TEMP3-2 of from -5 to 5°C.

10 11. The method according to one or more of claims 1 to 10, wherein STEP3 comprises a stirring STIRR3 of MIX3, STIRR3 is done for a time TIME3-2, TIME3-2 is from 1 to 12 h.

12. The method according to claim 11, wherein
15 STIRR3 is done after COOL3, with COOL3 as defined in claim 8.

13. The method according to claim 11 or 12, wherein STIRR3 is done at TEMP3-2, with TEMP3-2 as defined in claim 8.

20 14. The method according to one or more of claims 1 to 13, wherein 1,4-sorbitan is isolated in STEP4 from MIX3 by filtration.

15. The method according to one or more of claims 1 to 14, wherein STEP1, STEP2 and STEP3 are done consecutively in one and the same reactor.

25

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/072661

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D307/20
ADD.
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)
C07D
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 practicable, 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.
A	CN 106 167 476 A (GUANGZHOU CARDLO BIOCHEMICAL TECH CO LTD) 30 November 2016 (2016-11-30) cited in the application the whole document	1-15
A	US 2002/002284 A1 (DELGADO PETE [US] ET AL) 3 January 2002 (2002-01-03) cited in the application first step in the reaction scheme on page 5; page 7, paragraph 51	1-15
	----- -/--	

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search 10 October 2019	Date of mailing of the international search report 30/10/2019
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Guspanová, Jana

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2019/072661

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SOL SOLTZBERG ET AL: "Hexitol Anhydrides. Synthesis and Structure of Arlitan, the 1,4-Monoanhydride of Sorbitol 1", JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, vol. 68, no. 6, 1 June 1946 (1946-06-01), pages 919-921, XP055531609, ISSN: 0002-7863, DOI: 10.1021/ja01210a001 cited in the application preparation of Arlitan (1,4-sorbitan) in right column on page 920 -----	1-13
A	US 6 639 067 B1 (BRINEGAR WILLARD C [US] ET AL) 28 October 2003 (2003-10-28) column 3, line 45 - column 4, line 22; claims 1,7,8,15,16,27; figures 1,3; examples 1,4; table 2 -----	1-13
A	US 2016/130277 A1 (GOZLAN CHARLOTTE [FR] ET AL) 12 May 2016 (2016-05-12) cited in the application paragraphs [0033] - [0036]; example 1 -----	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2019/072661

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 106167476	A	30-11-2016	NONE

US 2002002284	A1	03-01-2002	US 2002002284 A1 03-01-2002
			US 2003013884 A1 16-01-2003
			US 2004063968 A1 01-04-2004

US 6639067	B1	28-10-2003	NONE

US 2016130277	A1	12-05-2016	CA 2914783 A1 18-12-2014
			CN 105873923 A 17-08-2016
			EP 3008059 A1 20-04-2016
			ES 2707959 T3 08-04-2019
			FR 3007031 A1 19-12-2014
			HU E041570 T2 28-05-2019
			JP 6322700 B2 09-05-2018
			JP 2016521724 A 25-07-2016
			US 2016130277 A1 12-05-2016
			WO 2014199345 A1 18-12-2014
