The process involves the reaction of Gamma cyclodextrin with phosphorous halide in the presence of organic solvent.
Specification

Title of the invention
5 IMPROVED PROCESS FOR PREPARATION OF SUGAMMADEX

Field of the invention
[0001] The present invention relates to an industrially viable, cost effective process for manufacturing 6-perdeoxy-6-per-halo Gamma Cyclodextrin, a key intermediate in the synthesis of Sugammadex.

Cross Reference to Related Application
[0002] This application is the complete specification and claims priority from the provisional specification No. 2459/CHE/2010 filed on 25.08.2010

Background of the invention
[0003] Sugammadex is a modified γ-cyclodextrin, with a lipophilic core and a hydrophilic periphery.

![Image of Sugammadex molecule]
Sugammadex (designation Org 25969, trade name Bridion) is an agent for reversal of neuromuscular blockade by the agent rocuronium in general anaesthesia. It is the first selective relaxant binding agent (SRBA). This gamma cyclodextrin has been modified from its natural state by placing eight carboxyl thio ether groups at the sixth carbon positions. These extensions extend the cavity size allowing greater encapsulation of the rocuronium molecule. These negatively charged extensions electrostatically bind to the positively charged ammonium group as well as contribute to the aqueous nature of the cyclodextrin. Sugammadex's binding encapsulation of rocuronium is one of the strongest among cyclodextrins and their guest molecules. The rocuronium molecule (a modified steroid) bound within Sugammadex's lipophilic core, is rendered unavailable to bind to the acetylcholine receptor at the neuromuscular junction. Sugammadex sodium contains 8 recurring glucose units each with 5 asymmetric carbon atoms, in total 40 asymmetric carbon atoms for the whole molecule.

The Sugammadex was disclosed in US6670340 by Akzo Nobel. The process for preparing Sugammadex is there outlined as follows: (Scheme-I)
In above process step-1 involves the preparation of Vilsmeier Hack reagent by the reaction of DMF, triphenylphosphine and Iodine. Drawback associated with this step is formation of triphenylphosphine oxide as a byproduct. Removal of triphenylphosphine oxide is very difficult from the reaction; it requires repeated washing with DMF under argon atmosphere and leads to inconsistency in yield of final product. Due to this, process is lengthy and not feasible on commercial scale.

The present invention provides improved conditions for carrying out step-1 in the above scheme, whereby the product of step-1 is obtained in better purity and yield than has previously been possible.
Summary of the invention

[0008] The invention is a novel process for the preparation of 6-perdeoxy-6-per-halo Gamma cyclodextrin which is a useful intermediate in the synthesis of Suggamadex, the process comprising of reacting Gamma cyclodextrin with phosphorous halide in presence of organic solvent. The 6-perdeoxy-6-per-halo Gamma cyclodextrin synthesized by the novel process is used in the preparation of Suggamadex.

[0009] The object of the present invention is to provide a novel process for the synthesis of 6-perdeoxy-6-per-halo Gamma Cyclodextrin, a useful intermediate in the synthesis of Suggamadex.

[0010] Another object of the present invention is to provide a process for producing 6-per-deoxy-6-per-(2-carboxyethyl)thio-y-cyclodextrin sodium salt (Suggamadex) by employing the 6-perdeoxy-6-per-halo Gamma Cyclodextrin synthesized by the present invention.

Description of the invention

[0011] In accordance with the present invention 6-perdeoxy-6-per-halo Gamma Cyclodextrin is obtained by the reaction of Gamma Cyclodextrin with phosphorous halide in an organic solvent. The process of the invention is depicted in following scheme-II
[0012] The Gamma Cyclodextrin which is the starting material for the present process is commercially available or can be synthesized by the teachings of the prior art.

[0013] Phosphorous halide is PX₅ or PX₃ where X is an F, Cl, Br and Iodine, preferable chlorine.

[0014] The organic solvent can be polar organic solvent consisting of CI-5 esters, acetonitrile, dimethylformamide, dimethylsulfoxide, preferably
dimethylformamide and the reaction is effectively carried out in between 60-100°C, preferably at 65-70°C.

[0015] In one embodiment, the present invention 6-perdeoxy-6-per-chloro Gamma Cyclodextrin (Formula-II-a) is obtained by the reaction of Gamma Cyclodextrin (Formula-I) with phosphorous pentachloride and dimethylformamide (DMF). The process of the invention is depicted in following scheme-III

![Scheme](image)

[0016] In the present invention Vilsmeier-Hack reagent is generated by reaction of DMF and PCls.

$$\text{PCl}_5 + \text{H}_2\text{C} = \text{N} = \text{C} = \text{H} \rightarrow \left[ \begin{array}{c} \text{H}_3\text{C} \\ \text{H}_3\text{C} \end{array} \right] \text{N}^{+} \text{Cl}^{-}$$

Vilsmeier Hack reagent

This reagent will react to gamma cyclodextrin to get halogenated product which is 6-perdeoxy-6-per-chloro Gamma Cyclodextrin. The reagent selectively reacts with per facial primary hydroxyl groups in presence of secondary hydroxys.

[0017] In another embodiment, the preparation of 6-per-deoxy-6-per-(2-carboxyethyl)thio-γ-cyclodextrin sodium salt (Suggamadex) comprising:
a) Reacting gamma-cyclodextrin (Formula-I) with phosphorous pentachloride and dimethylformamide to obtain 6-perdeoxy-6-per-chloro Gamma cyclodextrin (Formula-IIa).

b) 6-perdeoxy-6-per-chloro Gamma cyclodextrin (Formula-IIa) is reacted with 3-mercapto propionic acid in presence of alkali metal hydrides and an organic solvent to give 6-per-deoxy-6-per-(2-carboxyethyl)thio-y-cyclodextrin sodium salt. The process of the invention is depicted in following scheme-IV

[0018] The alkali metal hydrides are selected from the group consisting of sodium hydride, lithium hydride, potassium hydride preferably sodium hydride.
[0019] The advantage of the present process is that there is no formation of byproduct such as triphenylphosphine oxide, as present in prior art process. So, purification is not required which leads to better purity and yields for the intermediate as well as for final product.

[0020] Another advantage of the present invention is the significant difference between molecular weight of 6-per deoxy-6-per-chloro-γ-cyclodextrin (Mol. wt. 1444) and the final product (Mol. wt. 2178). The use of 6-per deoxy-6-per-chloro-γ-cyclodextrin instead of 6-per deoxy-6-per-bromo-γ-cyclodextrin (Mol. wt. 1800) in the final stage of the process would extend the scope of selection of appropriate dialysis membranes with precise molecular weight cut off and there by facilitate efficient purification of Sugammadex.

The invention is further illustrated with following non-limiting examples:

**Example: 1 Preparation of 6-perdeoxy-6-per-bromo Gamma Cyclodextrin**

[0021] A portion of phosphorous pentachloride (256.5 g) was added in DMF (300 ml) at 0-5°C. Mixture was stirred at 20-25°C for 1hr. A solution of gamma-cyclodextrin (50 g) in DMF (400ml) was added to above solution at 5-10°C under nitrogen. Mixture was stirred at 65-70°C 14 hrs. The reaction mixture was cooled to 20 - 25°C and DMF was removed under vacuum. The viscous residue was diluted with water. 5M NaOH solution was added dropwise to the above solution at 5-10°C until pH =8, the resulting slurry was stirred for one hour at 20-25°C. The slurry was filtered under vacuum and washed with water and dried. The crude product was diluted with water and resulting slurry was stirred at 20-25°C for one hour. The slurry was filtered under vacuum and the solid dried at 55-60°C under vacuum for 12hrs. (Yield - 94 - 98%, purity-98.5% by HPLC)

[0022] To a mixture of sodium hydride (24.4 g) in DMF (150 ml) at 0-5°C, a solution of 3-mercapto propionic acid (23.7 ml, 10 eq) in DMF (50 ml) was
added slowly under argon maintaining the temperature below 10 °C. The resulting mixture was stirred at 20 -25°C for 30 mins. Then 6-deoxy-6-chloro gamma cyclodextrin (40 g) in DMF (400 ml) was added slowly at 5-10°C under argon and the resulting mixture was heated to 70-75°C for 12 hrs. Reaction mixture was cooled to 20 -25°C and DMF removed partially under vacuum and the reaction mixture is diluted with ethanol (600 ml). The resulting precipitate was stirred at 20 - 25°C for 1 hr and filtered under vacuum and the solid dried to afford the crude Sugammadex (wet) (100 g). The crude product was purified over silica gel and sephadex G-25 column using water as eluent. (Yield 60%)
Claims

1. A process for preparing 6-perdeoxy-6-per-halo Gamma cyclodextrin (Formula-II) by reacting gamma-cyclodextrin (Formula-I) with phosphorous halide in presence of organic solvent

wherein X in Formula-II is F, Cl or Br or iodine but preferably X is chlorine.

2. The process according to claim 1, wherein the phosphorous halide is PX5 or PX3 where X is an F, Cl, Br or iodine and preferably X is chlorine.

3. The phosphorous halide used in the process according to claim 2 is PC15.

4. A process according to claim 1, wherein in the temperature is maintained from 60-100°C and preferably 65-70°C.

5. The organic solvent used in the process according to claim 1 is polar organic solvents selected from the group of polar aprotic solvents, C1-5 esters, acetonitrile, dimethylformamide or dimethylsulfoxide.

6. The process according to claim 5, wherein polar aprotic solvent is dimethylformamide.

7. A process for the preparation of 6-per-deoxy-6-per-(2-carboxyethyl)thio-y-cyclodextrin sodium salt comprising:
   a) reacting gamma-cyclodextrin (Formula-I) with phosphorous pentachloride and dimethylformamide to obtain 6-perdeoxy-6-per-chloro Gamma cyclodextrin (Formula-IIa);
b) reacting 6-perdeoxy-6-per-chloro Gamma cyclodextrin (Formula-IIa) with 3-mercapto propionic acid in presence of alkali metal hydrides and an organic solvent to give 6-per-deoxy-6-per-(2-carboxyethyl)thio-y-cyclodextrin sodium salt.

8. The step (b) of the process according to claim 7 is conducted in the presence of an alkali metal hydride selected from the group consisting of sodium hydride, Lithium hydride, potassium hydride and preferably sodium hydride.

9. A compound of formula (IIa) or a salt thereof consisting of the molecular structure as shown below:
10. The 6-perdeoxy-6-per-chloro gamma cyclodextrin (Formula-IIa) as claimed in claim 9 is used in the process for the preparation of Suggamadex.
**INTERNATIONAL SEARCH REPORT**

**INTERNATIONAL APPLICATION NO.**
PCT/IN2011/000562

**A. CLASSIFICATION OF SUBJECT MATTER**

See extra sheet
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)

IPC: C08B1/00, A61K1/00

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

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

CNPAT, WPI, EPDOC, CNKI: cyclodextrin, phosphorus trichloride, phosphorous chloride, phosphorous chloride, PC13, phosphorus]

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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| X A      | KAZIMIERZ CHMURSKI et al. An Improved Synthesis of 6-Deoxyhalo Cyclodextrins via
cyclohexylmethylpentachloride, phosphorus trichloride, phosphorous chloride, PC13, phosphorus| 9, 1-8, 10 |
|          | Halomethylpentamorpholinium Halides Vilsmeier-Haack Type Reagents. Tetrahedron Letters |

Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
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  *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)
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"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

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"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report
02 Feb. 2012 (02.02.2012)

Name and mailing address of the ISA/CN
The State Intellectual Property Office, the P.R.China
6 Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China 100088
facsimile No. 86-10-62019451

Authorized officer
LI, Zhe
Telephone No. (86-10)82245331

Form PCT/ISA/210 (second sheet) (July 2009)
## INTERNATIONAL SEARCH REPORT

Information on patent family members

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2011/000562

Continuation of: A. CLASSIFICATION OF SUBJECT MATTER
C08B37/16 (2006.01) i
A61K3 1/724 (2006.01) i