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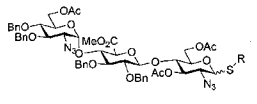
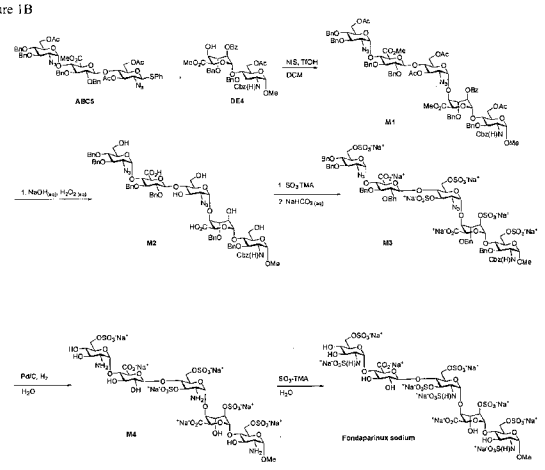


Figure 1B



(57) Abstract: The present invention provides novel processes for the preparation of Fondaparinux sodium by using the compound of formula ABC5. In some embodiments, the intermediates for the synthesis of Fondaparinux sodium, are also provided.

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Published:

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PROCESS FOR THE PRODUCTION OF FONDAPARINUX SODIUM

CROSS-REFERENCES TO RELATED APPLICATIONS

[0001] Not applicable

BACKGROUND OF THE INVENTION

[0002] Fondaparinux sodium (CAS 114870-03-0) is a member of oligosaccharides / heparins with a chemical name of O-[2-Deoxy-6-O-sulfo-2-(sulfoamino)-alpha-D-glucopyranosyl]-(1--4)-O-(beta-D-glucopyranurosonyl)-(1--4)-O-[2-deoxy-3,6-di-O-sulfo-2-(sulfoamino)-alpha-D-glucopyranosyl]-(1--4)-O-(2-O-sulfo-alpha-L-idopyranurosonyl)-(1--4)-O-[2-deoxy-1-O-methyl-6-O-sulfo-2-(sulfoamino)-alpha-D-glucopyranoside] decasodium salt, which developed by Choay, S.A. (see US 4,818,816). The compound is a synthetic pentasaccharide Factor Xa inhibitor which is indicated as an anticoagulant drug used for the prevention of deep vein thrombosis in patients who have had orthopedic surgery as well as for the treatment of deep vein thrombosis and pulmonary embolism. It was approved by the United States Food and Drug Administration in 2001, marketed under the trade name Arixtra™ which is administrated subcutaneously.

[0003] The preparation process of Fondaparinux sodium disclosed in U.S. Patent No. 4,818,816 is unsuitable for a large scale production since this process takes over 60 steps to afford a final product with low yield.

[0004] U.S. Patent No. 8,288,515 applies protection and de-protection steps to prepare Fondaparinux sodium. However, the de-protection step results in low yields and consumes additional reaction time.

[0005] Another process is disclosed in U.S. 2011/0306757, but the additional reduction step of an azide needs further purification and the final N-sulfonation step remains in low yield (68%).

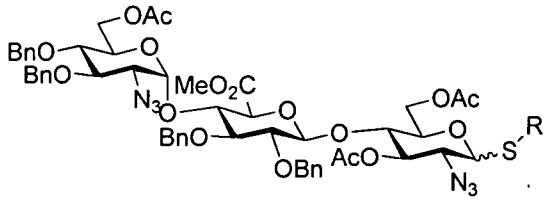
[0006] US 2012/0116066 describes the preparation of Fondaparinux sodium and its intermediates. However, the preparation of some intermediates such as EMod3 needs column purification. Moreover, the low α/β ratios in the coupling between C monomer and D monomer as well as numerous time-consuming procedures are not optimal.

[0007] In view of the above, there is still a need for a simple process with higher yield/purity for industrial preparation of Fondaparinux sodium.

BRIEF SUMMARY OF THE INVENTION

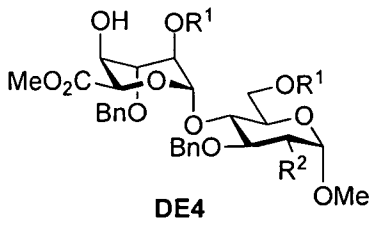
[0008] The present invention provides an economic process to prepare Fondaparinux sodium.

[0009] In one aspect, the present invention provides a novel process for the preparation of Fondaparinux sodium comprising reacting a compound of formula **ABC5**



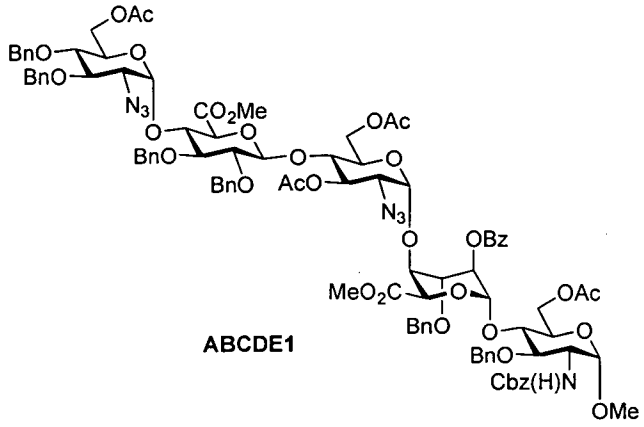
ABC5

with a compound of formula **DE4**



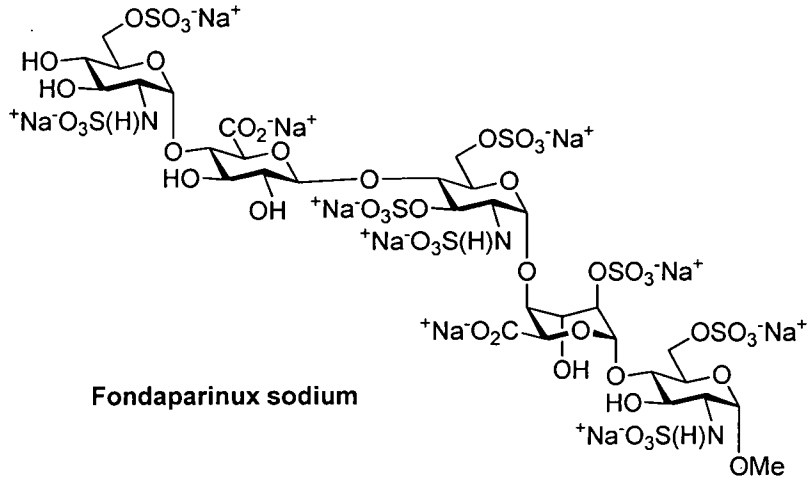
DE4

to obtain a compound of formula **ABCDE1**;



ABCDE1

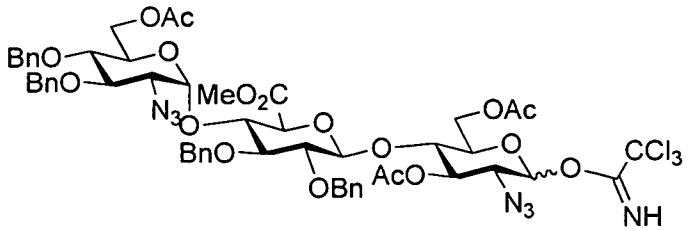
and then converting the compound of formula **ABCDE1** to Fondaparinux sodium.



Fondaparinux sodium

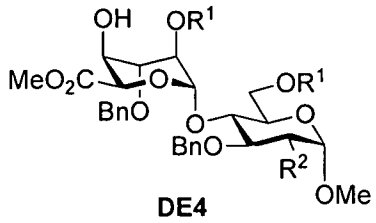
wherein R is selected from the group consisting of alkyl, phenyl, benzyl, substituted alkyl, substituted phenyl and substituted benzyl; R^1 is acetyl or benzyl; and R^2 is azide or NHCbz. The conversion of **ABCDE1** to Fondiparinux sodium is described below in the detailed description of the invention.

[0010] In the methods described herein, **ABCDE1** was initially prepared by reaction of donor trisaccharide **ABC4**



ABC4

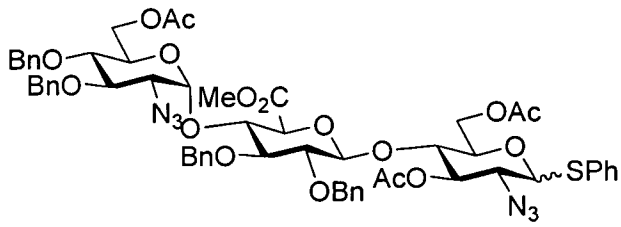
with acceptor disaccharide **DE4**,



DE4

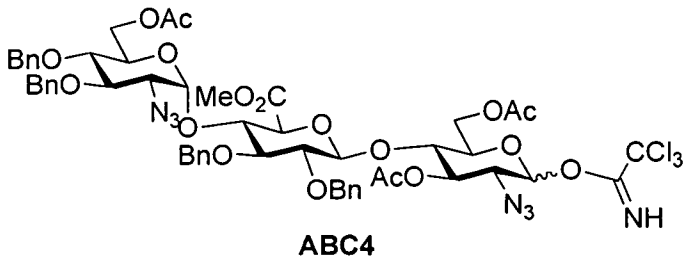
and obtained in 24% yield after being purified via column chromatography.

[0011] It was found that the trichloroacetimidate donor **ABC4** reacts rapidly with water which causes a reduced yield. Although the thio-donor (**ABC5**) is less active, a rapid reaction with H_2O can be avoided, which allows for a higher reaction yield. Surprisingly, the **ABCDE1** obtained from **ABC5**, especially phenylsulfanyl intermediate **ABC5a**, shown below, was isolated without column chromatography and the yield increased to 65 %.



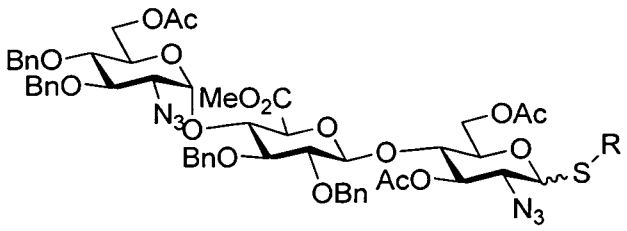
ABC5a

[0012] In a second aspect, the present invention provides a process for the preparation of a compound of formula **ABC5** comprising converting a compound of formula **ABC4**



ABC4

to the compound of formula **ABC5**



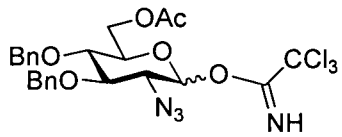
ABC5

in the presence of a promoter; wherein R is selected from the group consisting of alkyl, phenyl, benzyl, substituted alkyl, substituted phenyl and substituted benzyl.

[0013] The promoter is selected from the group consisting of trialkylsilyls, trifluoromethanesulfonates, and mixtures of trialkylsilyls and trifluoromethanesulfonates. In some embodiments, the promoter is selected from the group consisting of tert-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf), timethylsilyl trifluoromethanesulfonate (TMSOTf), triethylsilyl trifluoromethanesulfonate (TESOTf) and mixtures thereof.

[0014] In a third aspect, the present invention provides a process for the preparation of **ABC4** comprising:

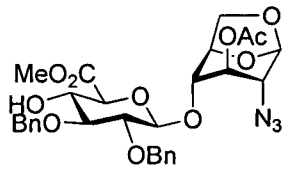
a) reacting the compound of formula **A5**



A5

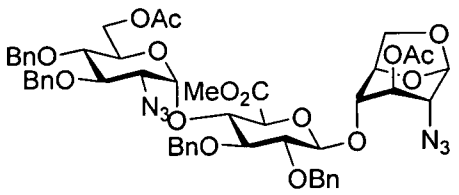
,

with a compound of formula **BC8**



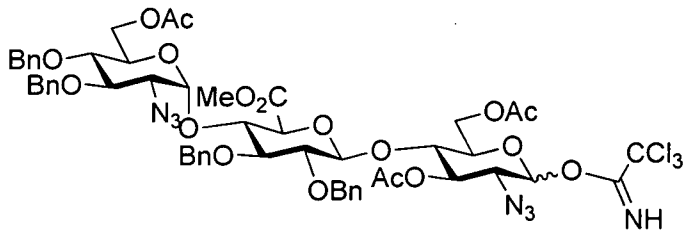
BC8

in an organic solvent in the presence of a promoter to provide a compound of formula **ABC1**



ABC1 ; and

b) converting the compound of formula **ABC1** to the compound of formula **ABC4**



ABC4

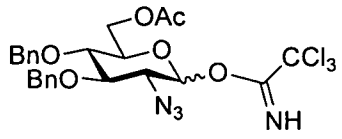
[0015] Preferably, the organic solvent used in step a) is selected from the group consisting of diethyl ether, methyl tert-butyl ether (MTBE), isopropyl ether (IPE), diglyme, toluene, xylenes and mixtures thereof. Preferably, the mixture is toluene/MTBE. More preferably, the ratio of toluene/MTBE is 0-30%. Most preferably, the ratio of toluene/MTBE is 15-25 %; still more preferably about 20%.

[0016] The α/β ratio of **ABC1** is improved by applying the solvent system of the present invention. For example, in toluene/MTBE, the result showed lower β form of **ABC1** (4-9%) than those obtained either from toluene/IPE (12%) or toluene/diglyme (18%).

[0017] Preferably, the promoter used in step a) is trimethylsilyl trifluoromethanesulfonate (TMSOTf), triethylsilyl trifluoromethanesulfonate (TESOTf), tert-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) and mixtures thereof. The collective individual trialkylsilyl triflates or mixtures thereof are also referred to herein as 'trialkylsilyls'. More preferably, the promoter is TBSOTf.

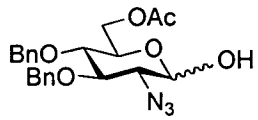
[0018] Step (b), i.e., the conversion of **ABC1** to **ABC4** is described below in the detailed description section.

[0019] In still another aspect, **A5**



A5

is prepared from **A4**



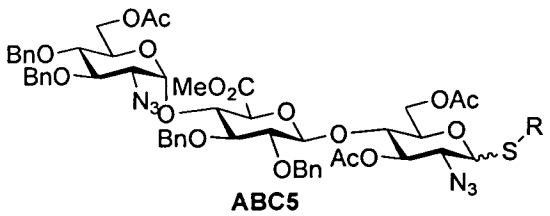
A4

in the presence of a base and trichloroacetonitrile.

[0020] Preferably, the base is selected from alkali carbonates such as sodium carbonate or potassium carbonate. More preferably, the base is potassium carbonate.

[0021] In US application Publication No. 2012/0116066, **A4** was reacted with trichloroacetonitrile and DBU to afford crude **A5**, after column purification, the yield was only 53%. Combining the next step wherein the product was reacted with **BC8**, the total yield of two steps was 34%. As provided in the present method, when DBU was replaced with an inorganic base such as K_2CO_3 (which can be easily filtered from organic solvent), the total yield of two steps improved to 62%.

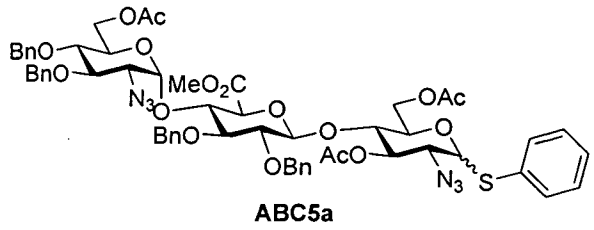
[0022] In a fourth aspect, the present invention provides a compound of formula **ABC5**



ABC5

wherein R is selected from the group consisting of alkyl, phenyl, benzyl, substituted alkyl, substituted phenyl and substituted benzyl.

[0023] In particular, **ABC5** is **ABC5a**.



ABC5a

BRIEF DESCRIPTION OF THE DRAWINGS

[0024] **Figures 1A and 1B** show an improved synthetic route for Fondaparinux sodium according to the present invention employing methods provided herein.

DETAILED DESCRIPTION OF THE INVENTION

I. General

[0025] The present invention provides a process for preparation of Fondaparinux sodium. The novel processes have been discovered to be of higher yield and with reduced impurity. The process provided herein also reduces the time required to complete numerous transformations (synthetic steps).

II. Definitions

[0026] As used herein, the term "contacting" refers to the process of bringing into contact at least two distinct species such that they can react. It should be appreciated, however, that the resulting reaction product can be produced directly from a reaction between the added reagents or from an intermediate from one or more of the added reagents which can be produced in the reaction mixture.

[0027] As used herein, the term "alkyl" by itself or as part of another substituent, means, unless otherwise stated, a straight or branched chain hydrocarbon radical. Alkyl substituents, as well as other hydrocarbon substituents, may contain number designators indicating the number of carbon atoms in the substituent (i.e., C_1-C_8 means one to eight carbons), although such designators may be omitted. Unless otherwise specified, the alkyl groups of the present

invention contain 1 to 12 carbon atoms. For example, an alkyl group can contain 1-2, 1-3, 1-4, 1-5, 1-6, 1-7, 1-8, 1-9, 1-10, 1-11, 1-12, 2-3, 2-4, 2-5, 2-6, 3-4, 3-5, 3-6, 4-5, 4-6 or 5-6 carbon atoms. Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl, sec-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, and the like.

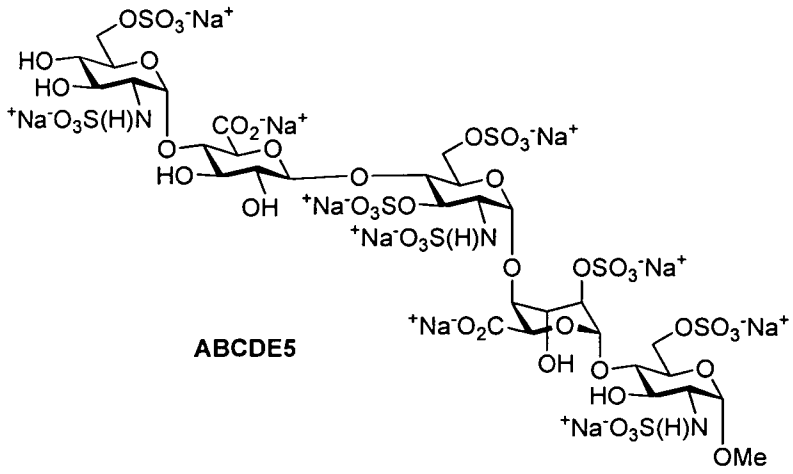
[0028] As used herein, the term 'substituted' when refering to alkyl, phenyl and benzyl, refers to one or more substituents, typically one to three substituents that are selected to be non-interfering substituents such as halogen, amino, hydroxy, nitro, cyano, lower alkyl (e.g., C_{1-4} alkyl), lower alkoxy (e.g., C_{1-4} alkyl-O-), lower alkylamino (e.g., C_{1-4} alkyl-NH-), di-lower alkylamino (e.g., di-C_{1-4} alkylamino), and haloalkyl. One of skill in the art will appreciate that additional substituted alkyl, phenyl and benzyl are known and useful in the context of the invention.

[0029] As used herein, a solvent mixture may comprise a percentage of a first solvent in a second solvent. Unless otherwise stated, the percentage is by volume.

[0030] Various protecting groups and protecting reagents, including hydroxyl protecting reagents, are well known to one of ordinary skill in the art and include compounds that are disclosed in *Protective Groups in Organic Synthesis*, 4th edition, T. W. Greene and P. G. M. Wuts, John Wiley & Sons, New York, 2006, which is incorporated herein by reference in its entirety.

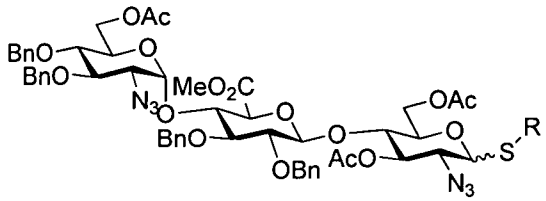
III. Embodiments of the Invention

[0031] In one aspect, the provided herein is a process for the preparation of Fondaparinux sodium of formula **ABCDE5**



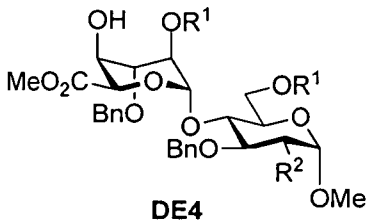
ABCDE5

comprising contacting a compound of formula **ABC5**



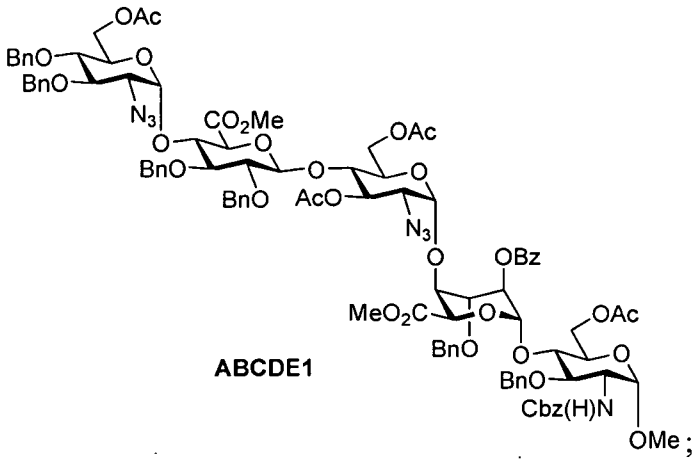
ABC5

with a compound of formula **DE4**



DE4

to obtain a compound of formula **ABCDE1**



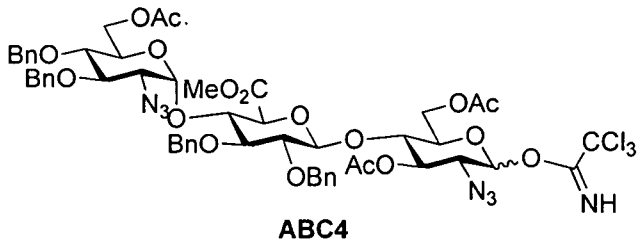
ABCDE1;

and then converting the compound of formula **ABCDE1** to Fondaparinux sodium;

wherein R is selected from the group consisting of alkyl, phenyl, benzyl, substituted alkyl, substituted phenyl, substituted benzyl; R^1 is acetal or benzyl; and R^2 is azide or NHCbz.

[0032] The conversion of **ABCDE1** to Fondaparinux sodium is described in more detail below.

[0033] In one group of embodiments, **ABC5** is obtained using a process comprising converting a compound of formula **ABC4**

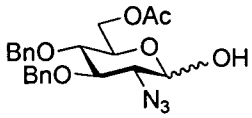


ABC4,

in the presence of a promoter and a thiol to provide the compound of formula **ABC5**. The promoters used in this group of embodiments are selected from the group consisting of TESOTf, TMSOTf, TfOH, TBSOTf and mixtures thereof.

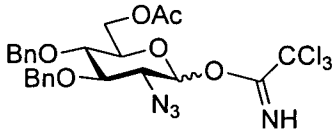
[0034] In another group of embodiments, **ABC4** is prepared from a process comprising:

a) converting a compound of formula **A4**



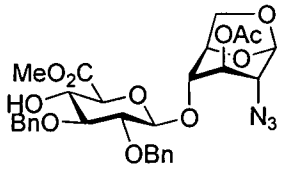
A4

to provide a compound of formula **A5**



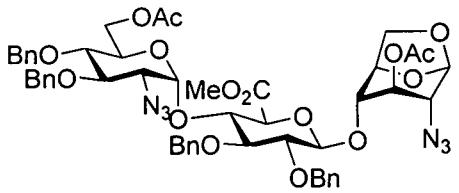
A5 ;

b) contacting the compound of formula **A5** with a compound of formula **BC8**



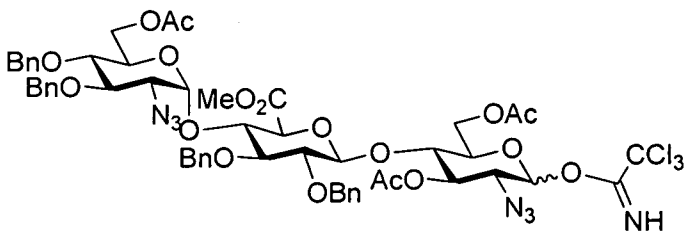
BC8

under conditions sufficient to provide a compound of formula **ABC1**



ABC1 ; and

c) converting the compound of formula **ABC1** to provide the compound of formula **ABC4**



ABC4

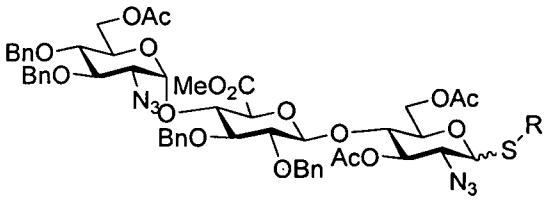
[0035] In step (a) above, the conversion of **A4** to **A5** is conducted in the presence of a base and trichloroacetonitrile. In one group of embodiments the base is an organic amine (e.g., DBU,

pyridine, triethylamine, diisopropylethyl amine, pyrrolidine, or any other such organic base). In another group of embodiments, the base is an inorganic base (e.g., potassium carbonate, sodium carbonate, potassium bicarbonate, sodium bicarbonate, cesium carbonate, potassium phosphate, or any other such inorganic base). A number of bases are useful in this conversion, particularly DBU, potassium carbonate and mixtures thereof. Preferably the base used is an alkali base.

[0036] In step (b) above, the contacting of **A5** with a compound of formula **BC8** to provide a compound of formula **ABC1** will generally take place in an organic solvent in the presence of a promoter. A variety of solvents are useful such as ether (e.g., diethyl ether, tetrahydrofuran), MTBE, IPE, diglyme, toluene, DCM, DCE and mixtures thereof. In one group of embodiments, the solvent is selected from diethyl ether, MTBE, IPE, diglyme, toluene, DCM and mixtures thereof. In one group of embodiments, the solvent is a mixture of 0-20% toluene or DCM in MTBE. In other embodiments, the solvent is a mixture of about 15-25% toluene in MTBE, more preferably about 20% toluene in MTBE. As with the above conversion of **ABC4** to **ABC5**, the promoters used in this group of embodiments are selected from the group consisting of TESOTf, TMSOTf, TfOH, TBSOTf and mixtures thereof.

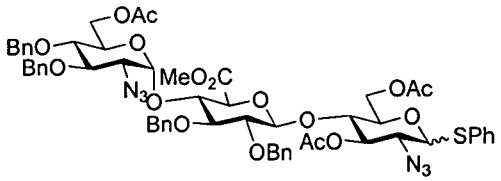
[0037] In step (c) above, the conversion of **ABC1** to a compound of formula **ABC4** will generally take place via a sequence of steps as follows. (c-1) Initially **ABC1** is converted to a ketal-hydrolysed product **ABC2** in the presence of a promoter, an organic solvent, a base and an acylating agent. Generally the reactions are carried out at about ambient temperature (e.g., from 20 °C to 30 °C), optionally at elevated temperatures. Suitable promoters include trialkylsilyls, trifluoromethanesulfonates, and mixtures of trialkylsilyls and trifluoromethanesulfonates. An exemplary ketal hydrolysis and anomeric acylation is provided in Example 2. (c-2) The acetyl group at the anomeric position in **ABC2** is cleaved in the presence of a base and an aprotic solvent to provide compound **ABC3**. Examples of aprotic solvents include toluene, xylenes, THF, EA, DCM, DCE and the like. An exemplary acetyl group cleavage is described in Example 3. (c-3) A leaving group is introduced at the anomeric position of **ABC3** to provide compound **ABC4**. Examples of suitable leaving groups include halogens, activated esters, acetimidates or the like. Generally the reaction is carried out in an aprotic solvent. Examples of aprotic solvents include toluene, xylenes, THF, EA, DCM, DCE and the like. An exemplary introduction of a trichloroacetimidate group (TCA) leaving group is provided in Example 4.

[0038] In another aspect, provided herein are novel intermediates having the formula **ABC5**:



ABC5 ;

wherein R is selected from the group consisting of alkyl, phenyl, benzyl, substituted alkyl, substituted phenyl and substituted benzyl. In one group of embodiments, a compound of formula **ABC5** described herein has the formula **ABC5a:**

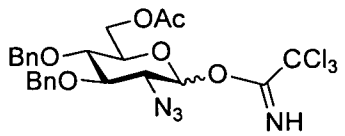


ABC5a .

[0039] In another group of embodiments, R in **ABC5** is substituted phenyl. In yet another group of embodiments, R in **ABC5** is benzyl or substituted benzyl. In further embodiments, R in **ABC5** is alkyl or substituted alkyl.

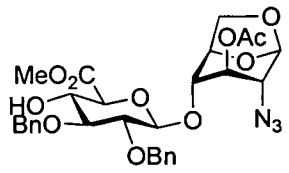
[0040] Also provided herein is a process for preparing Fondaparinux sodium comprising:

i) contacting the compound of formula **A5**



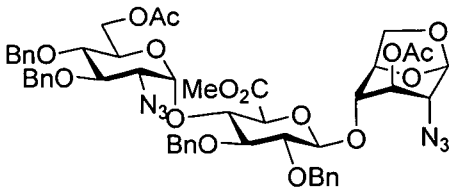
A5 ,

with the compound of formula **BC8**



BC8

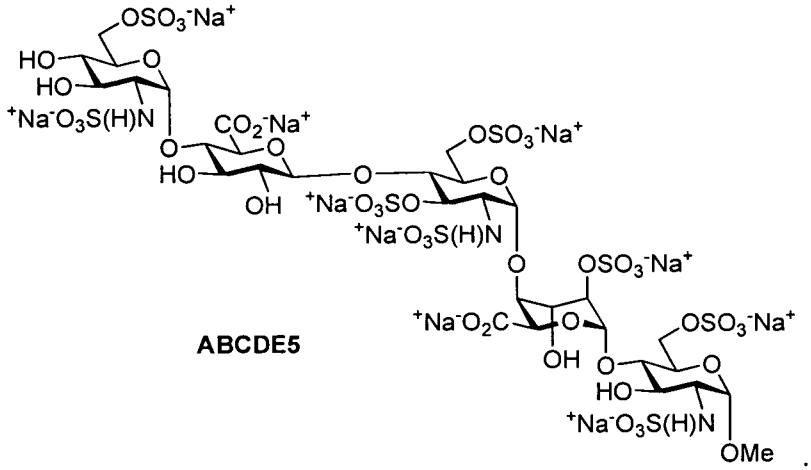
to provide the compound of formula **ABC1**



ABC1

in a mixture of toluene/MTBE; and

ii) converting the compound of formula **ABC1** to provide Fondaparinux of formula **ABCDE5**:



ABCDE5

[0041] In one group of embodiments, step (i) above is conducted in toluene/MTBE in the presence of a base. In certain embodiments, the base is an organic amine (e.g., DBU, pyridine, triethylamine, diisopropylethyl amine, pyrrolidine, or any other such organic base). In another group of embodiments, the base is an inorganic base (e.g., potassium carbonate, sodium carbonate, potassium bicarbonate, sodium bicarbonate, cesium carbonate, potassium phosphate, or any other such inorganic base).

[0042] In step (ii) above, the conversion of **ABC1** to **ABCDE5** is achieved via a series of reactions as follows. (ii-1) Initially **ABC1** is converted to a ketal-hydrolysed product **ABC2** in the presence of a promoter, an organic solvent, a base and an acylating agent. Generally the reactions are carried out at about ambient temperature (e.g., from 20 °C to 30 °C), optionally at elevated temperatures. Suitable promoters include trialkylsilyls, trifluoromethanesulfonates, and mixtures of trialkylsilyls and trifluoromethanesulfonates. An exemplary ketal hydrolysis and anomeric acylation is provided in Example 2. (ii-2) The acetyl group at the anomeric position in

ABC2 is cleaved in the presence of a base and an aprotic solvent to provide compound **ABC3**. Examples of aprotic solvents include toluene, xylenes, THF, EA, DCM, DCE and the like. An exemplary acetyl group cleavage is described in Example 3. (ii-3) A leaving group is introduced at the anomeric position of **ABC3** to provide compound **ABC4**. Examples of suitable leaving groups include halogens, activated esters, acetimidates or the like. Generally the reaction is carried out in an aprotic solvent. Examples of aprotic solvents include toluene, xylenes, THF, EA, DCM, DCE and the like. An exemplary introduction of a trichloroacetimidate group (TCA) leaving group is provided in Example 4. (ii-4) A thio-donor compound **ABC5** is generated from **ABC4** by reaction of **ABC4** with a thiol in the presence of a promoter in an organic solvent. Generally the reaction is carried out in an aprotic solvent. Examples of aprotic solvents include toluene, xylenes, THF, EA, DCM, DCE and the like. Suitable promoters include trialkylsilyls, trifluoromethanesulfonates, and mixtures of trialkylsilyls and trifluoromethanesulfonates. An exemplary introduction of a thiophenyl group is described in Example 4. Generally the reaction mixture includes a base. Examples of bases include organic bases such as triethylamine, diisopropylamine, diisopropylethylamine and the like, or inorganic bases such as potassium carbonate, sodium carbonate, cesium carbonate and the like. One of skill in the art will understand that the introduction of a thio-donor moiety is possible under various conditions and depends on the leaving group present in the compound. (ii-5) The thio donor compound **ABC5** is reacted with an acceptor compound such as **DE4** to obtain an oligosaccharide **ABCDE1**. The reaction is carried out in the presence of a radical initiator and/or a promoter in an organic solvent. Generally the reaction is carried out in an aprotic solvent. Examples of aprotic solvents include toluene, xylenes, THF, EA, DCM, DCE and the like. The reaction is generally carried out at a temperatures ranging from about -30 °C to about 40 °C. Suitable promoters include trialkylsilyls, trifluoromethanesulfonates, and mixtures of trialkylsilyls and trifluoromethanesulfonates. Non-limiting examples of radical initiators include N-iodosuccinimide, N-bromosuccinimide and the like. An exemplary reaction between a donor and an acceptor compound is shown in Example 5. One of skill in the art will understand that the donor-acceptor reaction is possible under various conditions and depends on the thio-donor moiety and the acceptor moiety present in the compounds.

[0043] The conversion of **ABCDE1** to **ABCDE5** is achieved as follows. (ii-6) The ester group in **ABCDE1** is cleaved in the presence of a peroxide and a base in an aprotic solvent to

provide **ABCDE2**. Examples of aprotic solvents include toluene, xylenes, THF, EA, DCM, DCE and the like. The reaction is generally carried out initially at temperatures below 10 °C, then warmed to ambient temperature (e.g., 20 °C to 30 °C). Example 6 provides an exemplary procedure for ester cleavage in an oligosaccharide. (ii-7) **ABCDE2** is then O-sulfated in the presence of a base to provide **ABCDE3**. The reaction is generally carried out in an aprotic solvent by introduction of sulfate groups using a sulfating reagent, followed by addition of a base to introduce counterions for the sulfate groups. Example 7 provides an exemplary procedure for introduction of sodium sulfate groups. (ii-8) The Cbz protecting group in **ABCDE3** is removed under suitable conditions to provide **ABCDE4**. In some cases, hydrogenation is used which also reduces the azido groups to amine groups. The hydrogenation is typically carried out at ambient temperatures (e.g., 20 °C to 30 °C) for a period of 1-5 days, preferably 1-3 days. Example 8 provides an exemplary procedure for conversion of **ABCDE3** to **ABCDE4**. (ii-9) **ABCDE4** is converted to Fondaparinux via an N-sulfation step, using a sulfating reagent, followed by addition of a base to introduce counterions for the sulfate groups. The compound is then desalted. Example 9 provides an exemplary procedure for introduction of sodium sulfate groups. The sodium salt is desalted in the final step to obtain Fondaparinux.

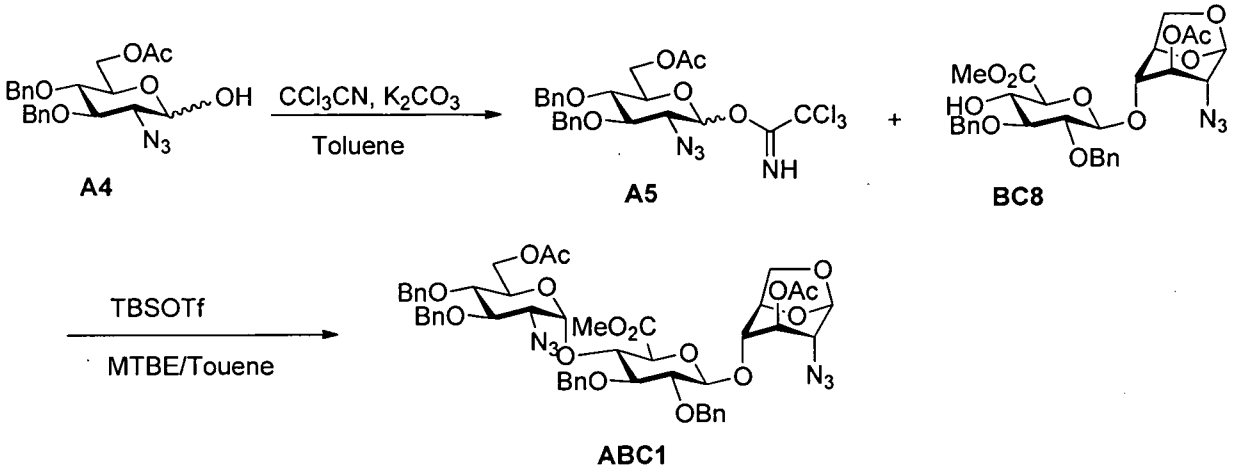
[0044] In a select group of embodiments, a solvent mixture for the reaction of **A5** with **BC8** in step (i) above is a toluene/MTBE mixture having a ratio of toluene/MTBE from 10% to 30%, or from 15% to 25%, preferably 20%.

EXAMPLES

[0045] The following examples are presented to describe the invention in further detail. However, the present invention is by no means restricted to the specific embodiments described herein. The following abbreviations are used in the specification, and examples: DCM is dichloromethane; EA is ethyl acetate; THF is tetrahydrofuran; MTBE is methyl *tert*-butyl ether; DMAc is dimethylacetamide; OTCA is a trichloroacetimidate group; DCE is dichloroethane; IPE is isopropyl ether; CBz is carboxybenzyl, a carbamate protecting group. Compound **BC8** can be prepared according to U.S. application publication no. 20120083594. Compound **A4** can be prepared according to procedures in *J. Am Chem Soc.*, 2005, **127**, 3767-3773; or Tetrahedron: Asymmetry, 2005, **16**(2), 411 – 424.

Example 1

Preparation of ABC1



A4 to **A5**

[0046] A four-necked round bottom flask was equipped with a mechanical stirrer and a thermometer. To the flask was added **A4** (32 g, 75 mmol, 1.4 equiv), toluene (64 mL), K_2CO_3 (52 g, 374 mmol, 7.0 equiv), and CCl_3CN (37 mL, 374 mmol, 7.0 equiv) at 20-30°C under nitrogen. The mixture was stirred at 20-30°C for 4 hr. The mixture was filtered and the filtered cake was washed with toluene (64 mL). The filtrate and washing were combined to afford **A5** in toluene solution. After being cooled to no more than –10°C, the **A5**/toluene solution was ready to be used.

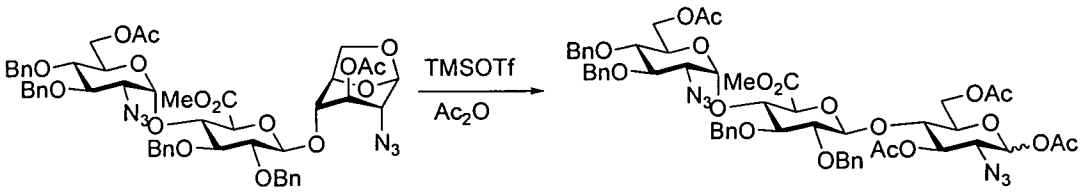
BC8 to **ABC1**

[0047] A four-necked round bottom flask was equipped with a mechanical stirrer and a thermometer. To this flask was added **BC8** (32 g, 53 mmol, 1 equiv) and MTBE (576 mL) at 20-30°C under nitrogen. The mixture was heated to no more than 45°C for dissolution. After being cooled to 20-30°C, 3Å molecular sieves (15 g) were added to the mixture and the resulting mixture was stirred at this temperature for 2 hr. The mixture was then cooled to –35 to –25°C. TBSOTf (5 mL, 21 mmol, 0.4 equiv) was added at –35 to –25°C, and the mixture was stirred at this temperature for about 15 min. The resulting mixture containing **BC8** and 3Å molecular sieves in MTBE was ready to be used.

[0048] To the flask containing **A5**/toluene solution was added into the mixture containing **BC8** and 3Å molecular sieves in MTBE over 30 min while maintaining temperature at –35 to –25°C. The mixture was stirred at –35 to –25°C for 1 hr. Triethylamine (23 mL, 160 mmol, 3 equiv) and Ac_2O (5 mL, 53 mmol, 1 equiv) were successively added at –35 to –25°C. The mixture was heated to about 50°C and stirred for 6 hr. The mixture was filtered and the filtered cake was washed with MTBE (64 mL). The filtrate and washing were combined and concentrated to afford crude **ABC1** solution. Crude **ABC1** solution was purified using column chromatography (silica gel; eluting solvent: EtOAc/ n-heptane(first eluting solvent is 1:4 and then 2:3)) and then concentrated to afford **ABC1** solution (50 g, 88%) in EtOAc / n-heptane (1/1(v/v)).

Example 2

Preparation of ABC2

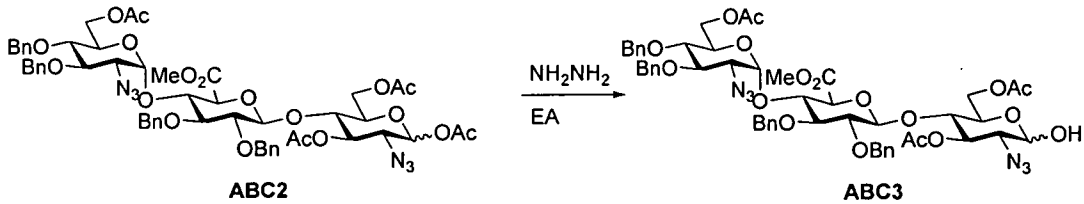


ABC1 ABC2

[0049] A three-necked round bottom flask was equipped with a mechanical stirrer and a thermometer. To the flask was added the previously reserved **ABC1** in EtOAc / n-heptane solution (162mL, 1/1(v/v)) at 20-30°C under nitrogen. After the mixture was cooled to 0-10°C, Ac_2O (16.3 g, 0.16 mol, 3.0 equiv) and TMSOTf (3.6 g, 0.02 mol, 0.3 equiv) were successively added at this temperature. The mixture was stirred at 0-10°C for not less than 10 hr. Triethylamine (45 mL, 0.27 mol, 6.0 equiv) was slowly added at 0-10°C. The mixture was stirred at 0-10°C for 1 hr. 20% $NaCl_{(aq)}$ (64 mL, 2 vol) was slowly added at 0-10°C. The mixture was stirred for 2 hr. The separated aqueous portion was discarded. The separated organic portion containing **ABC2** in EtOAc / n-heptane (1/1 (v/v)) solution was ready to be used in the next step.

Example 3

Preparation of ABC3



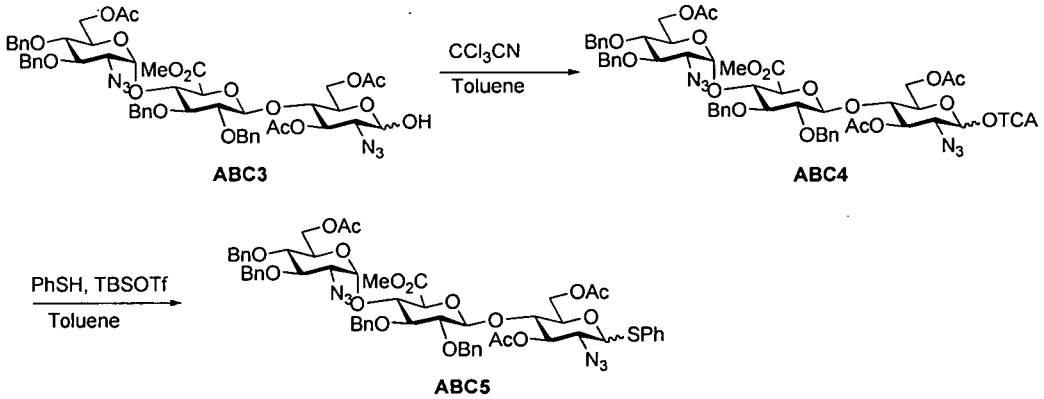
ABC2 ABC3

[0050] A three-necked round bottom flask was equipped with a mechanical stirrer and a thermometer. To the flask was added the previously reserved **ABC2** in EtOAc / n-heptane (1/1

(v/v)) solution at 20-30°C under nitrogen. H_2NNH_2-H_2O (3.8 g, 80 mmol, 1.4 equiv) was added at 20-30°C, and the mixture was stirred at this temperature for 3 hr. A 5% solution of $NaCl_{(aq)}$ (160 mL) was added at 20-30°C, and the mixture was stirred at this temperature for 1 hr. The stirring was stopped for phase separation. The separated aqueous phase was discarded. The organic and emulsion portions were combined and concentrated to afford crude **ABC3** in EtOAc / n-heptane solution. Crude **ABC3** solution was purified with column chromatography (silica gel; eluting solvent: acetone/ toluene (containing 0.05%(v/v) of Et_3N, 5/95(v/v))) and then concentrated to afford **ABC3** in toulene solution (44 g, 94%).

Example 4

Preparation of ABC5



ABC3 to **ABC4**

[0051] A four-necked round bottom flask was equipped with a mechanical stirrer and a thermometer. To the flask was added **ABC3**/toluene solution (about 96 mL, 3 vol) at 20-30°C under nitrogen. K_2CO_3 (74 g, 0.53 mol, 10 equiv) and CCl_3CN (77 g, 0.53 mol, 10 equiv) were successively added at 20-30°C. The mixture was stirred at 20-30°C for not less than 4 hr. The mixture was filtered and the filtered cake was washed with toluene (64 mL, 2 vol). The filtrate and washing were combined to afford **ABC4** in toluene solution. After being cooled to no more than –5°C, the **ABC4**/toluene solution (about 160 mL, 5 vol) was ready to be used.

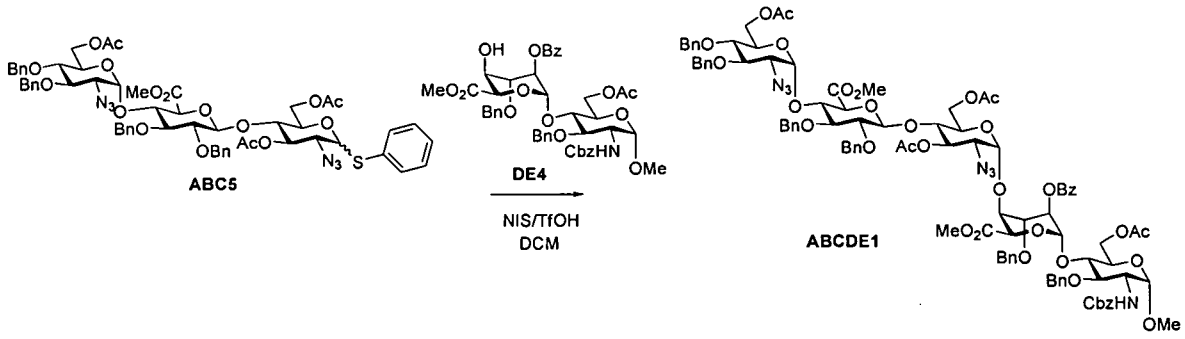
ABC4 to **ABC5**

[0052] A four-necked round bottom flask was equipped with a mechanical stirrer and a thermometer. To the flask was added thiophenol (24 g, 0.2 mmol, 4 equiv) and toluene (260 mL) at 20-30°C under nitrogen. The mixture was cooled to –20 to –10°C. TBSOTf (21 g, 0.08 mol, 1.5 equiv) was added at –20 to –10°C. The resulting mixture containing thiophenol and TBSOTf in toluene was ready to be used.

[0053] To the flask containing **ABC4** solution was added the mixture containing thiophenol and TBSOTf in toluene over 30 min while maintaining temperature at –20 to –10°C. The mixture was stirred at –20 to –10°C for 2 hr. Et_3N/toluene (15 mL/65 mL) was slowly added over about 30 min while maintaining temperature no more than –5°C. The mixture was stirred at no more than –5°C for 30 min. The mixture was concentrated to afford crude **ABC5** solution in toluene. **ABC5** solution was purified with column (silica gel; eluting solvent: EtOAc/ toulene (containing 0.05% (v/v) of Et_3N, 2/98, (v/v))) to afford **ABC5** in toulene solution (42 g, 88%).

Example 5

Preparation of ABCDE1



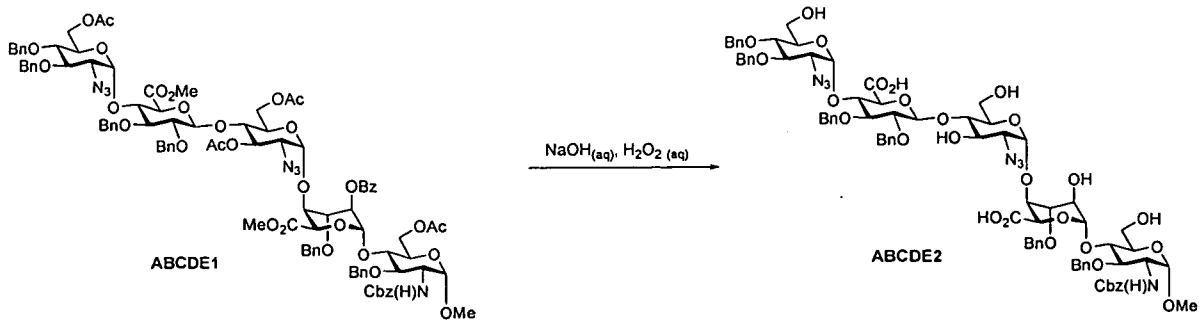
[0054] **ABC5** (35 g, 0.03 mol, 1.0 equiv), **DE4** (28 g, 0.033 mol, 1.1 equiv), and DCM (700 g,) were added into a four-necked round bottom flask equipped with a mechanical stirrer and a thermometer at 20-40°C under nitrogen. The mixture was stirred at 20-40°C for 30 min to obtain a homogeneous solution. 3Å molecular sieves (35 g) was added at 20-40°C, and the mixture was stirred at this temperature for 1 hr.

[0055] After the mixture was cooled to –30 to –20°C, N-iodo-succinimide (NIS) (10.2 g, 1.5 equiv, 0.045 mol) was added at this temperature and stirred for 15 min. TfOH (1.8 g, 0.012 mol, 0.4 equiv) in DCM (10 mL) was slowly added at –30 to –20°C, and the mixture was stirred at this temperature for 2 hr. Et_3N (6.1 g, 0.06 mol, 2 equiv) was added at –30 to –20°C, and the mixture was stirred at this temperature for 30 min. The mixture was filtered through a celite pad, and the filtered cake was washed with DCM (140 mL). The combined filtrate and washing was added 30% $Na_2S_2O_3 \cdot 5H_2O_{(aq)}$ (105 mL, 3 vol) at 20-40°C. After the mixture was stirred at 20-40°C for 1 hr, the stirring was stopped for about 5 min to effect phase separation. The separated aqueous portion was discarded. The separated organic portion was concentrated to afford crude **ABCDE1** solution in DCM. Crude **ABCDE1** solution was purified with column chromatography (silica gel; eluting solvent: EtOAc/ toulene (containing Et_3N (0.1% (v/v)) 1/9(v/v)) to provide a solution of **ABCDE1** in toulene solution.

[0056] **ABCDE1** in toulene solution (about 105 mL) was added into a four-necked round bottom flask equipped with a mechanical stirrer and a thermometer under nitrogen. After the mixture was heated to 35-45°C, IPA (105 mL) and *n*-heptane (105 mL) were sequentially added at this temperature. **ABCDE1** seed (0.035 g) was added at 35-45°C, and the mixture was stirred at this temperature for 1 hr. After *n*-heptane (175 mL) was added at 35-45°C, the mixture was cooled to 15-25°C and stirred for 1hr. The mixture was filtered and the filtered cake was washed with *n*-heptane (70 mL). The wet cake was dried at no more than 60°C to afford **ABCDE1** (39 g, 65%) as a white solid.

Example 6

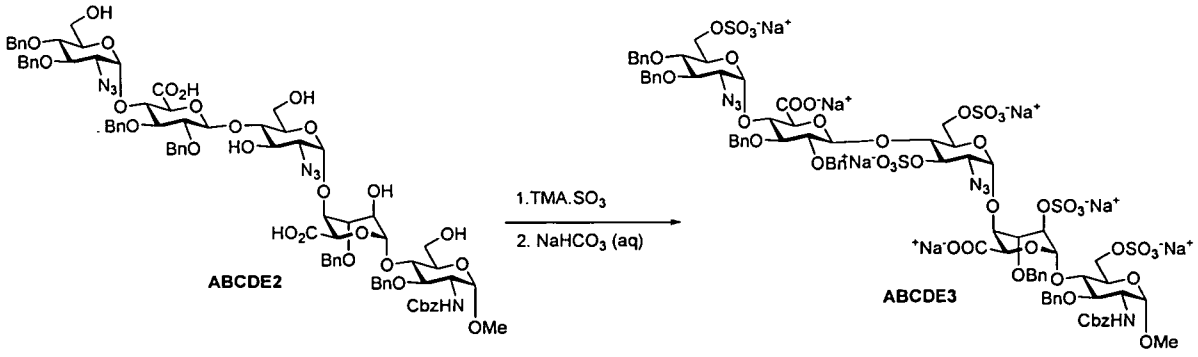
Preparation of ABCDE2



[0057] THF (250 mL) and **ABCDE1** (50 g, 26.4 mmol, 1.0 equiv) were charged into a four-necked round bottom flask at 20-40°C under nitrogen. The mixture was cooled to 10°C, and 35% $H_2O_{2(aq)}$ (102.5 mL, 1161 mmol, 44 equiv) was added at this temperature. 2N $NaOH_{(aq)}$ (356 mL, 712.4 mmol, 27 equiv) was added at 10°C. The mixture was heated to 20-30°C and stirred for 48 hr. The stirring was stopped for about 5 min to affect phase separation. The separated organic portion was saved, and the separated aqueous portion was discarded. The reserved organic portion was added 30% $Na_2S_2O_3 \cdot 5H_2O_{(aq)}$ (250 mL, 5 vol), and the mixture was stirred for about 5 min. The stirring was stopped for about 5 min to affect phase separation. The separated organic portion was saved, and the separated aqueous portion was discarded. The reserved organic portion was added 30% $Na_2S_2O_3 \cdot 5H_2O_{(aq)}$ (250 mL, 5 vol), and the mixture was stirred for about 5 min. The stirring was stopped for about 5 min to affect phase separation. The separated organic portion was saved, and the separated aqueous portion was discarded. The reserved organic portion was added H_2O (500 mL, 10 vol), and 1N $HCl_{(aq)}$ (45 mL, 0.9 vol) was added till pH of the mixture reached 4-5. Acetone (250 mL, 5 vol) was added and the mixture was concentrated at 35-60°C to a volume of about 700 mL. 1N $HCl_{(aq)}$ (5 mL) was added to reach a pH of the mixture of about 2.5-3.5. After being stirred at 20-30°C for 30 min, the mixture was filtered and the filtered cake was washed with H_2O (250 mL). The wet cake was dried at no more than 60°C to afford **ABCDE2** as white solid (38.4 g, 82% yield).

Example 7

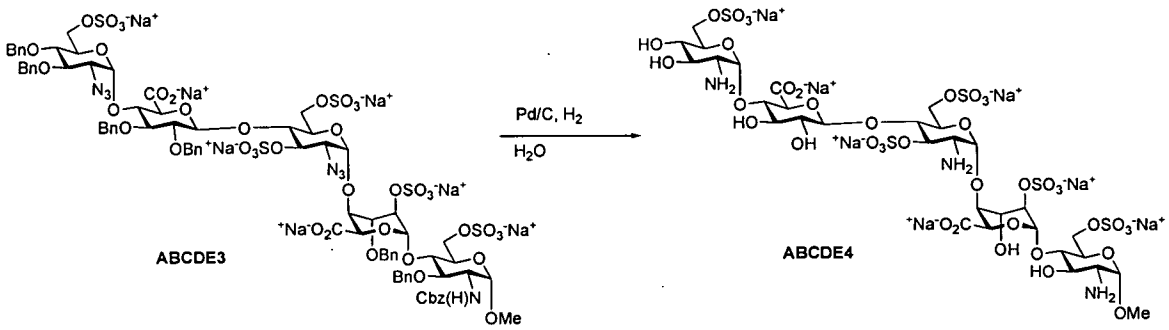
Preparation of ABCDE3



[0058] **ABCDE2** (8 g, 1.0 equiv, 5.02 mmol), SO_3-TMA complex (38.4 g, 55 equiv, 275.92 mmol), and DMAc (88 mL) were added into a round bottom flask equipped with a mechanical stirrer and a thermometer under nitrogen at 20-40°C. The slurry mixture was heated to 55-65°C and stirred for 6 hr. After being cooled to no more than 10°C, to the mixture was added 8% $NaHCO_{3(aq)}$ (40 mL) at no more than 30°C. The mixture was filtered and the filtered cake was washed with DMAc (96 mL). After the combined filtrate and washing was cooled to no more than 10°C, water(88 mL) was slowly added while maintaining temperature at 30°C. A mixture containing crude **ABCDE3** solution DMAc/ water was thus obtained. **ABCDE3** was purified with HP20SS resin by eluting solvent via $NaCl_{(aq)}$ (10%) and then MeOH and then solvent exchanged by water to afford **ABCDE3** aqueous solution.

Example 8

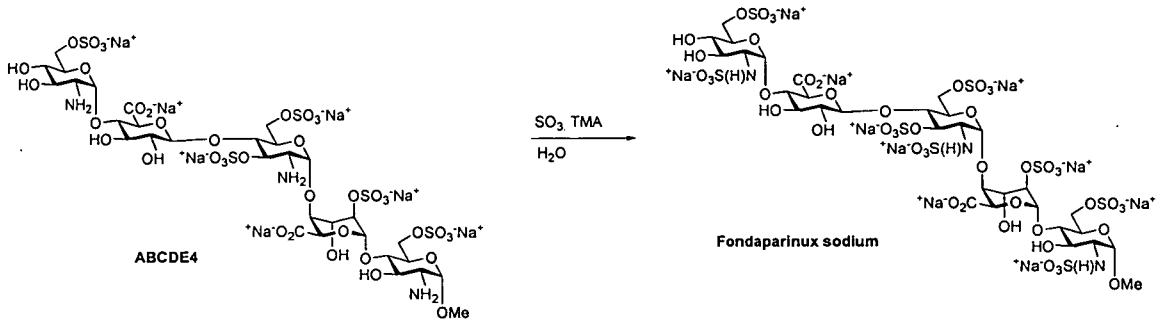
Preparation of ABCDE4



[0059] **ABCDE3** aqueous solution (based on 8 g of **ABCDE2**), and 10% Pd/C (3.2 g, 40% wt) were added into an autoclave at 20-30°C. The mixture was exposed to hydrogen (0-0.5 kg, gauge pressure) at 20-30°C for 48 hr. The mixture was filtered through a celite pad, and the filtered cake was washed with water (32 mL). After the combined filtrate and washing was added activated charcoal (1.6 g,) at 20-30°C, the mixture was stirred at this temperature for 3 hr. The mixture was filtered through a celite pad, and the filtrate was saved. The reactor was rinsed with PPW (32 mL), and the solution was filtered through a 0.2 micrometer filter. The two filtrates were combined to afford a **ABCDE4** aqueous solution.

Example 9

Preparation of Fondaparinux



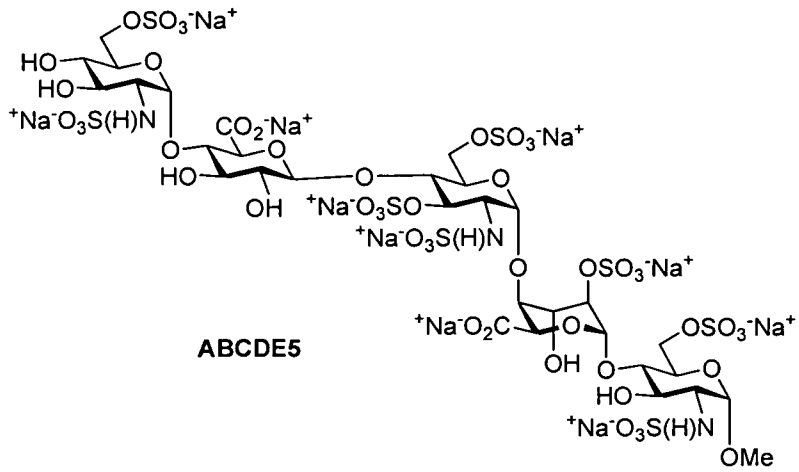
[0060] **ABCDE4** aqueous solution (based on 8 g of **ABCDE2**) was added into a round bottom flask equipped with a mechanical stirrer and thermometer at 20-40°C. The mixture was added 1N $HCl_{(aq)}$ till pH reached 8-9. After SO_3•TMA (23.04 g, 33 equiv, 165.5 mmol) was added at 20-40°C, the mixture was heated to 40-50°C and stirred for 10 hr. The mixture was cooled to no more than 10°C. The mixture was filtered and the filtered cake was washed with water (32 mL). The filtrate was added 1N $NaOH_{(aq)}$ till pH reached 9-10. The mixture was heated to 45-55°C and stirred for 20 hr. The mixture was cooled to no more than 30°C. A mixture containing crude Fondaparinux sodium aqueous solution was thus obtained.

[0061] Crude Fondaparinux sodium aqueous solution (2.4 g) was purified with Q Sepharose Fast Flow resin (QSFF) (190 mL) using the eluting solvent via 0.4M $NaCl_{(aq)}$, 0.8M $NaCl_{(aq)}$ and 2M $NaCl_{(aq)}$ to afford Fondaparinux sodium solution. Fondaparinux sodium was desalted by 0.1 m^2 of 1 kDa regenerous cellulose (RC) membrane using Tangential Flow Filtration (TFF) and then lyophilized to afford Fondaparinux (2.2 g, 80%).

[0062] Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity of understanding, one of skill in the art will appreciate that certain changes and modifications may be practiced within the scope of the appended claims. In addition, each reference provided herein is incorporated by reference in its entirety to the same extent as if each reference was individually incorporated by reference. Where a conflict exists between the instant application and a reference provided herein, the instant application shall dominate.

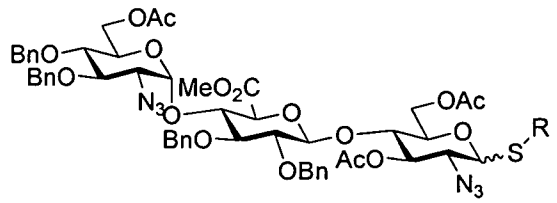
WHAT IS CLAIMED IS:

1. A process for the preparation of Fondaparinux sodium of formula **ABCDE5**



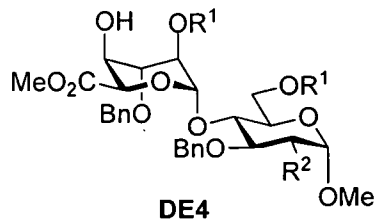
ABCDE5

comprising contacting a compound of formula **ABC5**



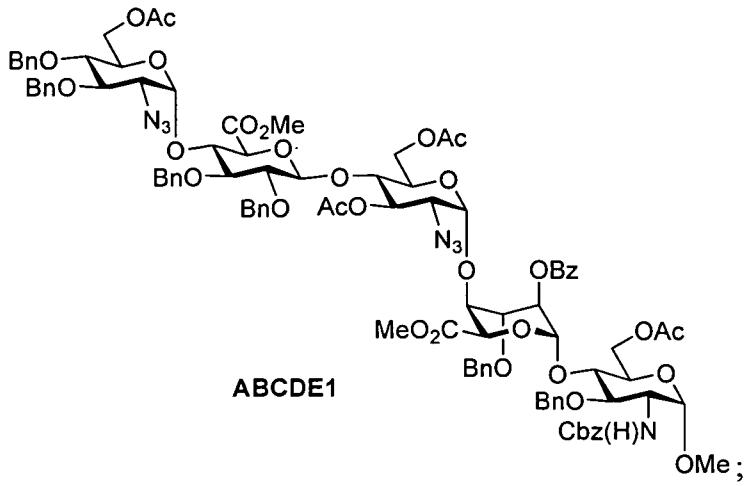
ABC5

with a compound of formula **DE4**



DE4

to obtain a compound of formula **ABCDE1**



ABCDE1

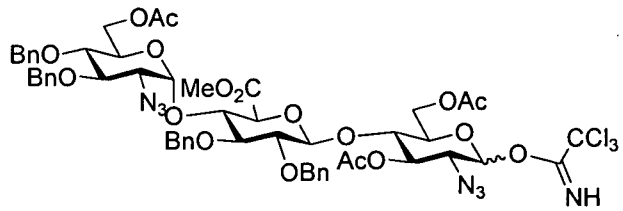
and then converting the compound of formula **ABCDE1** to Fondaparinux sodium; wherein

R is selected from the group consisting of alkyl, phenyl, benzyl, substituted alkyl, substituted phenyl, substituted benzyl; and

R^1 is acetal or benzyl; and

R^2 is azide or NHCbz.

2. A process of claim **1**, wherein **ABC5** is obtained using a process comprising converting a compound of formula **ABC4**

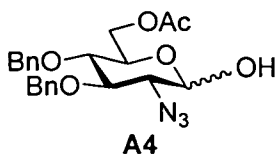


ABC4

in the presence of a promoter to provide the compound of formula **ABC5**.

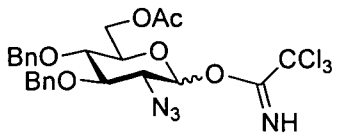
3. A process of claim **2**, wherein **ABC4** is prepared from a process comprising:

a) converting a compound of formula **A4**:



A4

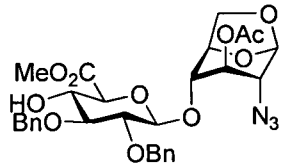
to a compound of formula **A5**:



A5

;

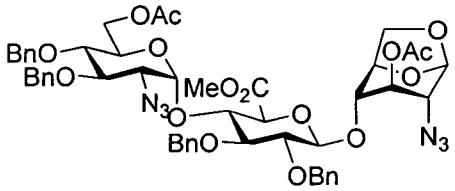
b) contacting the compound of formula **A5** with a compound of formula **BC8**:



BC8

;

to provide a compound of formula **ABC1**:



ABC1

; and

c) converting the compound of formula **ABC1** to the compound of formula **ABC4**.

4. A process of claim **3**, wherein step a) is conducted in the presence of a base and trichloroacetonitrile.

5. A process of claim **4**, wherein the base is selected from the group consisting of DBU and potassium carbonate.

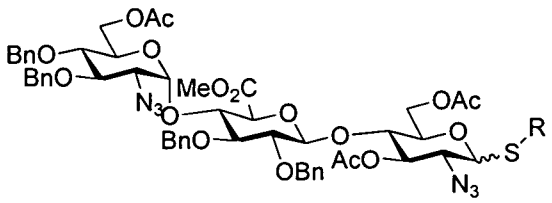
6. A process of claim **3**, wherein step b) is conducted in an organic solvent in the presence of a promoter.

7. A process of claim **6**, wherein the organic solvent is selected from the group consisting of diethyl ether, methyl tert-butyl ether, isopropyl ether, diglyme, toluene, DCM and mixtures thereof.

8. A process of claim **7**, wherein the mixture is 0-20% toluene or 0-20% dichloromethane (DCM) in methyl *tert*-butyl ether (MTBE) by volume of solvent mixture.

9. A process of claim **2** and **6**, wherein the promoter is selected from the group consisting of TESOTf, TMSOTf, TfOH, TBSOTf and mixtures thereof.

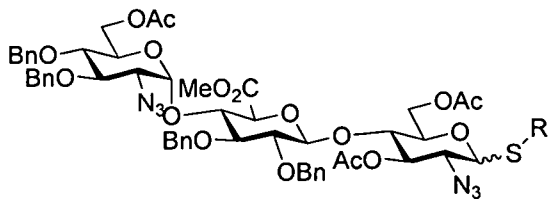
10. A compound of formula **ABC5**



ABC5 ;

wherein R is selected from the group consisting of alkyl, phenyl, benzyl, substituted alkyl, substituted phenyl and substituted benzyl.

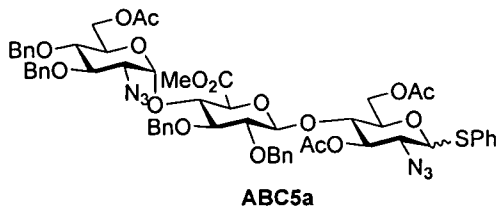
11. A compound having the formula **ABC5**:



ABC5 ;

wherein R is selected from the group consisting of alkyl, phenyl and benzyl.

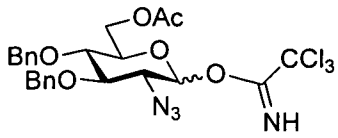
12. A compound of claim **11**, wherein **ABC5** is **ABC5a**:



ABC5a

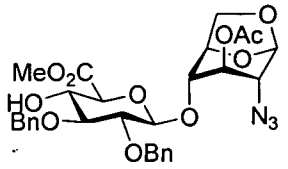
13. A process for preparing Fondaparinux sodium comprising:

i) contacting the compound of formula **A5**



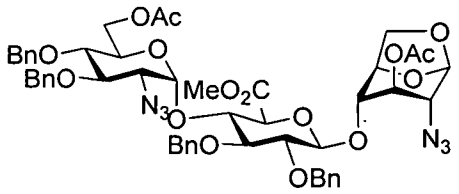
A5

with the compound of formula **BC8**



BC8

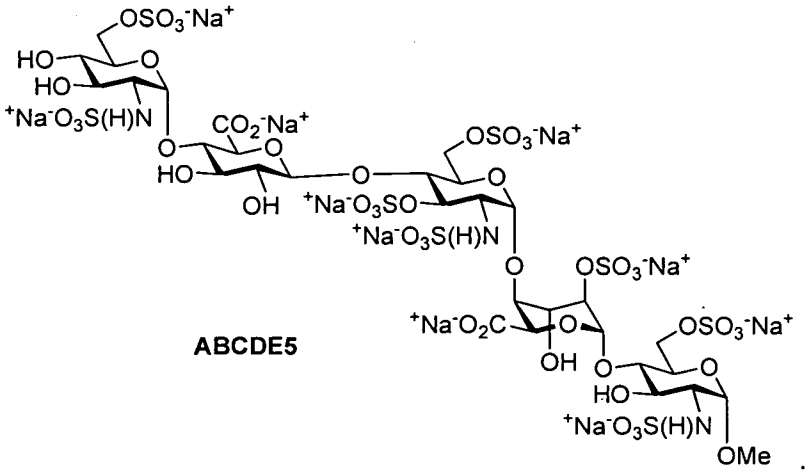
to provide the compound of formula **ABC1**



ABC1

in a mixture of toluene/MTBE; and

ii) converting the compound of formula **ABC1** to Fondaparinux of formula **ABCDE5**:



ABCDE5

14. The process of claim **13**, wherein the ratio of toluene/MTBE is about 20%.

Figure 1A

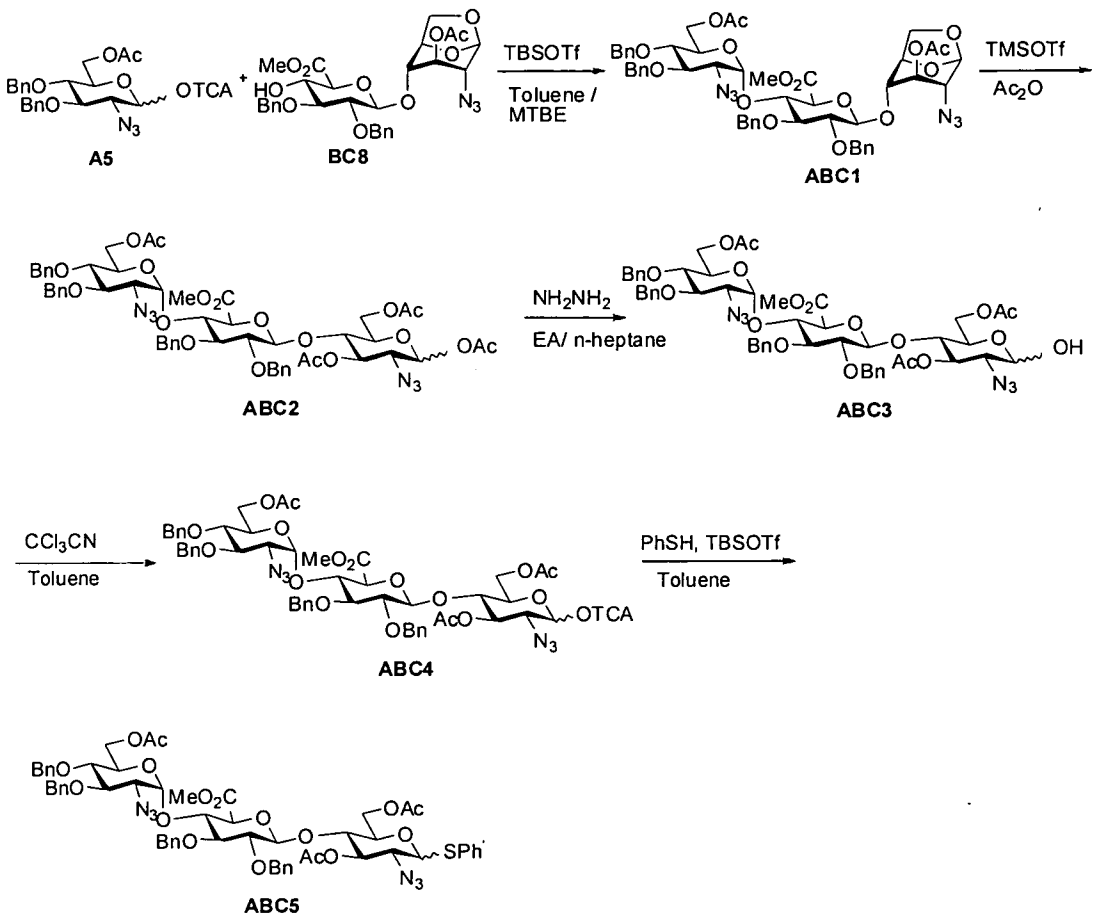
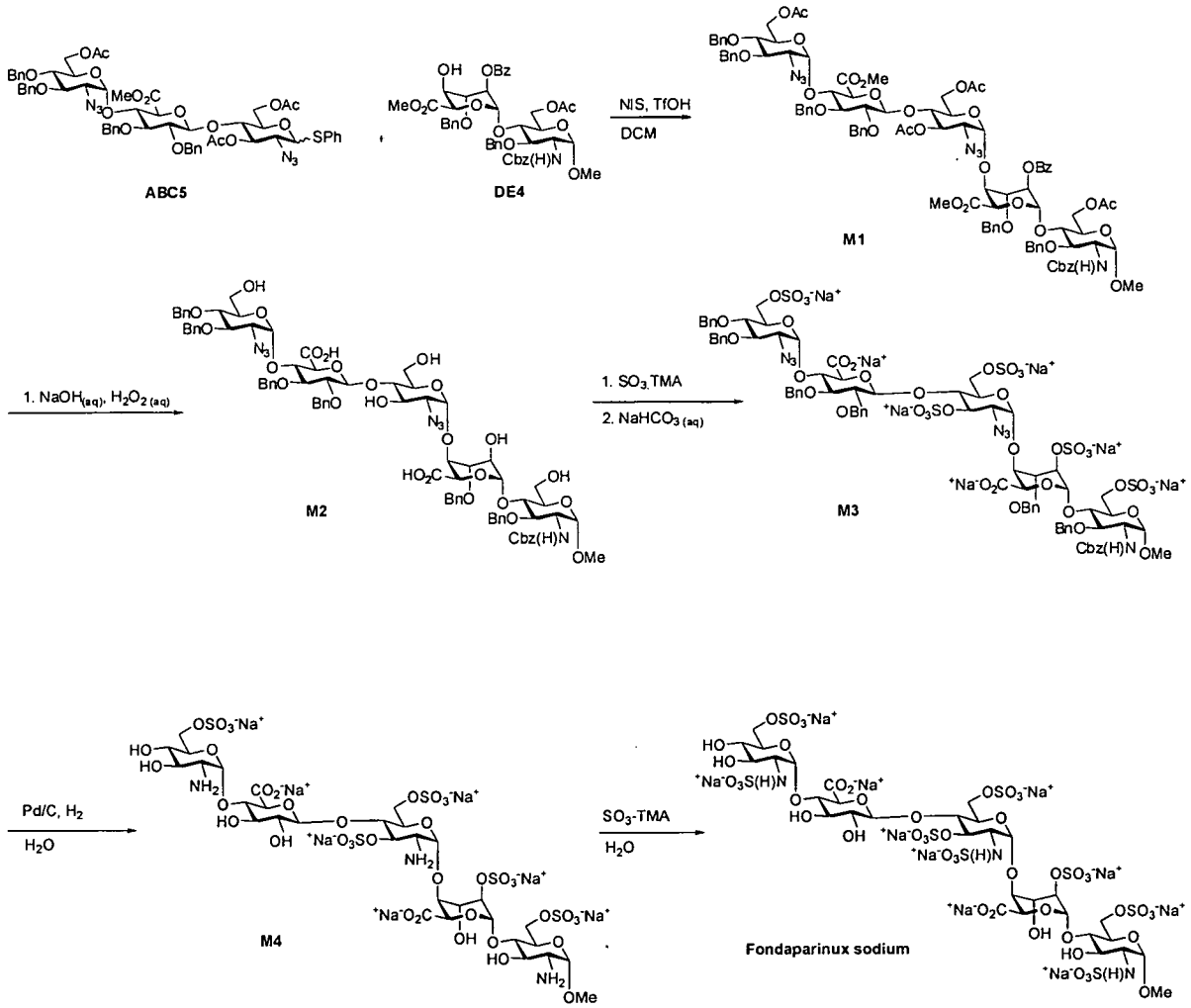

A5
BC8
TBSOTf
Toluene / MTBE
ABC1
TMSOTf
Ac2O
ABC2
NH2NH2
EA/ n-heptane
ABC3
CCl3CN
Toluene
ABC4
PhSH, TBSOTf
Toluene
ABC5

Figure 1B


ABC5
DE4
NIS, TfOH
DCM
M1
1. NaOH(aq), H2O2 (aq)
M2
1. SO3.TMA
2. NaHCO3 (aq)
M3
Pd/C, H2
H2O
M4
SO3-TMA
H2O
Fondaparinux sodium

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2013/002161

A. CLASSIFICATION OF SUBJECT MATTER

C07H 15/18(2006.01)i, C07H 1/06(2006.01)i, A61K 31/7024(2006.01)i

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 15/18; C08B 37/10; C07H 7/06; C07H 11/00; C07H 5/10; C07H 1/00; C07H 15/04; C07H 1/06; A61K 31/7024

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: fondaparinux sodium, trisaccharide, pentasccharide, preparation

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2013-0005954 A1 (KOVI, RAVISHANKER et al.) 03 January 2013 See abstract and paras. 45-47.	1-14
A	US 2012-0208993 A1 (SEIFERT, JOACHIM et al.) 16 August 2012 See abstract and para. 31.	1-14
A	US 2012-0116066 A1 (PATEL, PAYAL P. et al.) 10 May 2012 See abstract and paras. 21-25, 153-154, 160-162 and 205.	1-14
A	US 2011-0306757 A1 (LOPEZ-BELMONTE ENCINA, IVAN et al.) 15 December 2011 See the whole document.	1-14
A	US 8288515 B2 (NADJI, SOURENA et al.) 16 October 2012 See the whole document.	1-14

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
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"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	Date of mailing of the international search report
23 April 2014 (23.04.2014)	**23 April 2014 (23.04.2014)**

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/IB2013/002161

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