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(54) Title: PROCESS FOR PREPARATION OF ERIBULIN AND INTERMEDIATES THEREOF

(57) Abstract: The present application relate to process for preparation of octahydropyrano [3, 2-b] pyran compound of formula II, which is useful as an intermediate for the preparation of halichondrin B analogues such as Eribulin or its pharmaceutically acceptable salts.



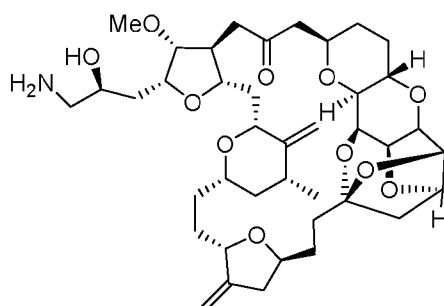
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PROCESS FOR PREPARATION OF ERIBULIN AND INTERMEDIATES THEREOF

INTRODUCTION

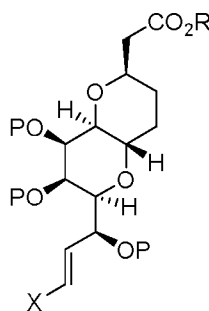
Aspects of the present application relate to process for preparation of octahydropyrano [3, 2-b] pyran compound of formula II, which is useful as an intermediate for the preparation of halichondrin B analogues such as Eribulin or its pharmaceutically acceptable salts.

The drug compound having the adopted name Eribulin, is a synthetic analogue of halichondrin B, and is represented by structure of formula I.



I

Eribulin is a microtubule inhibitor indicated for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. U.S. Patent No. 6,214,865 discloses eribulin and its pharmaceutically acceptable salts. Octahydropyrano [3, 2-b] pyran compound of formula II used as an intermediate for the preparation of halichondrin B analogues such as Eribulin.



II

wherein P is an alcohol protected group, X is a halogen and R is C₁-C₈ alkyl group;

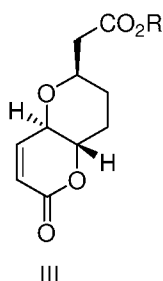
Process for the preparation of hexahydropyrano [3, 2-b] pyran compound of formula II have been disclosed in U.S. patent No. 5,338,865 and *Tetrahedron Letters*, 1996 Vol. 37, No. 48, pp. 8643-8646. The reported processes suffer from major

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disadvantages, including use of highly expensive reagents, large amounts of catalysts, low temperature, longer reaction time and use of column chromatography for purifications. Hence, there remains a need to provide an alternative processes for the preparation of octahydropyrano [3, 2-b] pyran compound of formula II, which is simple, economic and industrially viable.

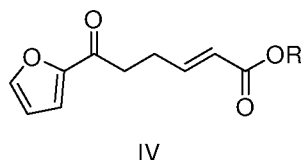
SUMMARY

In the first embodiment, the present application provides a process for preparation of hexahydropyrano pyran compound of formula III,



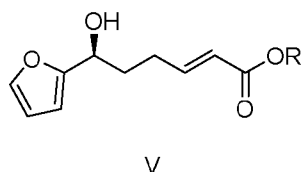
wherein R is C₁-C₈ alkyl group; which includes one or more of the following steps:

(a) converting furan or 2-acetyl furan to a compound of formula IV;



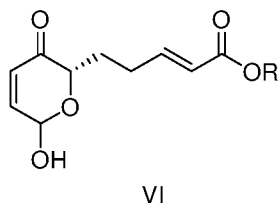
wherein R is C₁-C₈ alkyl group;

(b) reducing compound of formula IV to hydroxy compound of formula V;



wherein R is C₁-C₈ alkyl group;

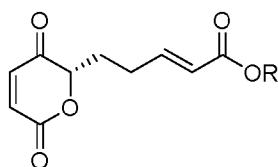
(c) converting hydroxy compound of formula V to pyran compound of formula VI;



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wherein R is C₁-C₈ alkyl group;

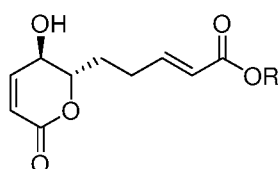
(d) oxidizing compound of formula VI to provide compound of formula VII;



VII

wherein R is C₁-C₈ alkyl group;

(e) reducing the compound of formula VII to provide hydroxy compound of formula VIII; and

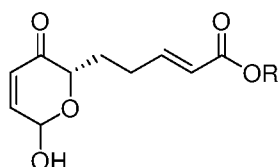


VIII

wherein R is C₁-C₈ alkyl group;

(f) converting hydroxy compound of formula VIII to hexahydropyrano pyran compound of formula III.

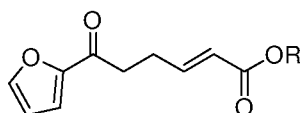
In the second embodiment, the present application provides a process for preparation of pyran compound of formula VI,



VI

wherein R is C₁-C₈ alkyl group; which comprises:

(a) converting furan or 2-acetyl furan to a compound of formula IV;

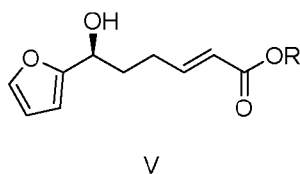


IV

wherein R is C₁-C₈ alkyl group;

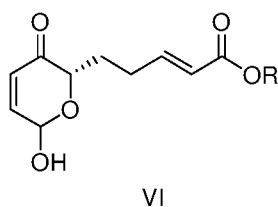
(b) reducing compound of formula IV to hydroxy compound of formula V;

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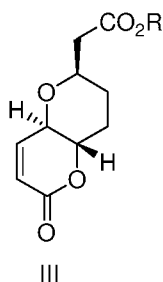
wherein R is C₁-C₈ alkyl group;

(c) converting hydroxy compound of formula V to pyran compound of formula VI;



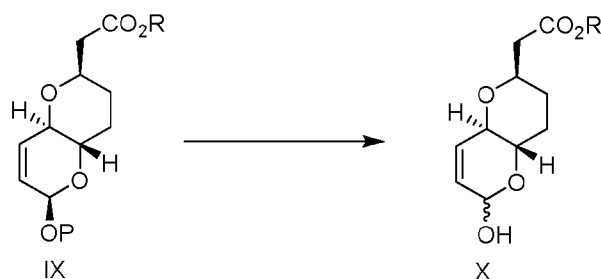
wherein R is C₁-C₈ alkyl group.

In the third embodiment, the present application provides a process for preparation of compound of formula III comprising:



wherein R is C₁-C₈ alkyl group;

(a) deprotecting compound of formula IX to provide compound of formula X;

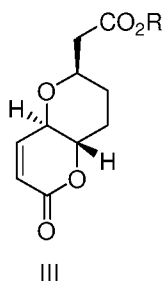


wherein R is C₁-C₈ alkyl group, P is an alcohol protected group;

(b) oxidizing compound of formula X to provide compound of formula III.

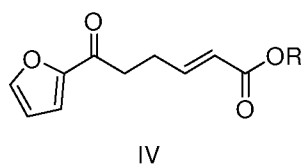
In the fourth embodiment, the present application provides a process for preparation of compound of formula III,

-5-



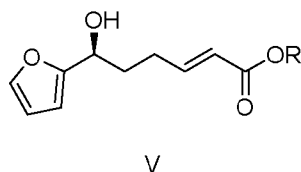
wherein R is C₁-C₈ alkyl group; which comprises:

(a) converting furan or 2-acetyl furan to a compound of formula IV;



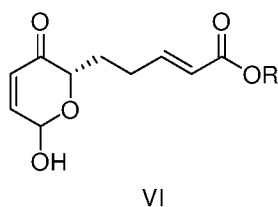
wherein R is C₁-C₈ alkyl group;

(b) reducing compound of formula IV to hydroxy compound of formula V;



wherein R is C₁-C₈ alkyl group;

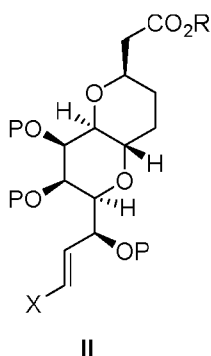
(c) converting hydroxy compound of formula V to pyran compound of formula VI;



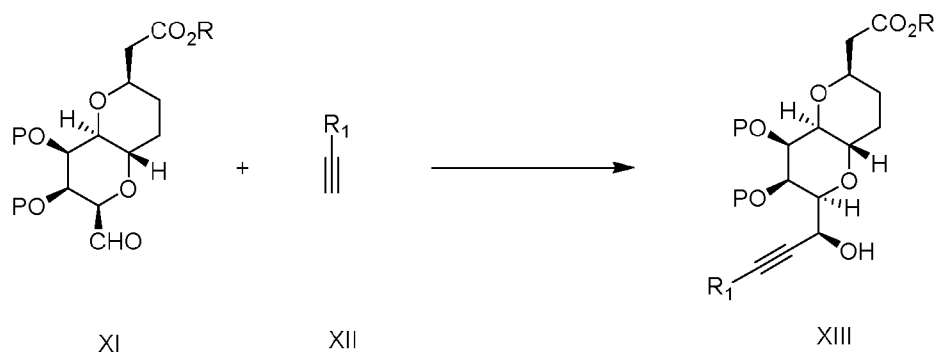
wherein R is C₁-C₈ alkyl group.

In the fifth embodiment, the present application provides a process for preparation of octahydropyrano [3, 2-b] pyran compound of formula II,

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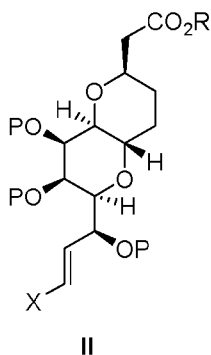


wherein P is an alcohol protected group, X is a halogen and R is C₁-C₈ alkyl group; which comprises: treating aldehyde compound of formula XI with compound of formula XII to provide compound of formula XIII;



wherein R is C₁-C₈ alkyl group, R₁ is trialkyl silyl and P is an alcohol protecting group.

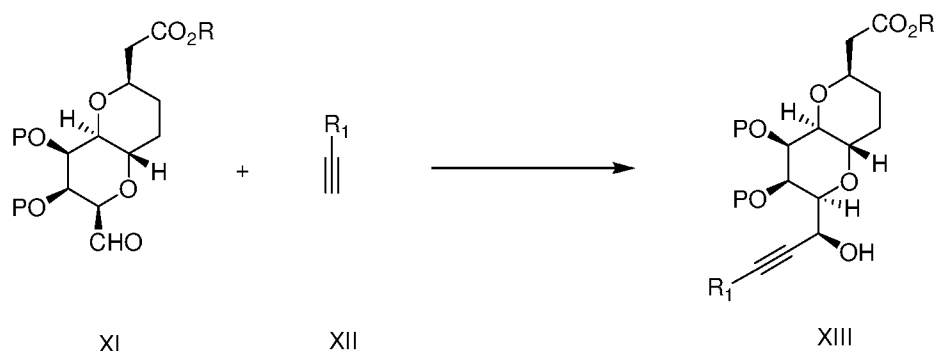
In the sixth embodiment, the present application provides a process for preparation of octahydropyrano [3, 2-b] pyran compound of formula (II),



Wherein R is C₁-C₈ alkyl group, P is alcohol protecting group and X is a halogen; which includes one or more of the following steps:

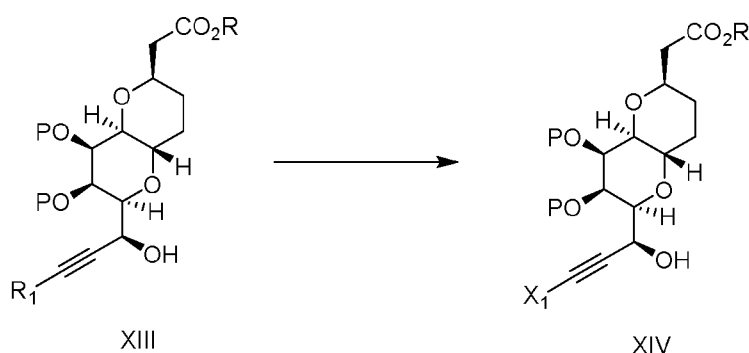
(a) treating aldehyde compound of formula XI with compound of formula XII to provide compound of formula XIII;

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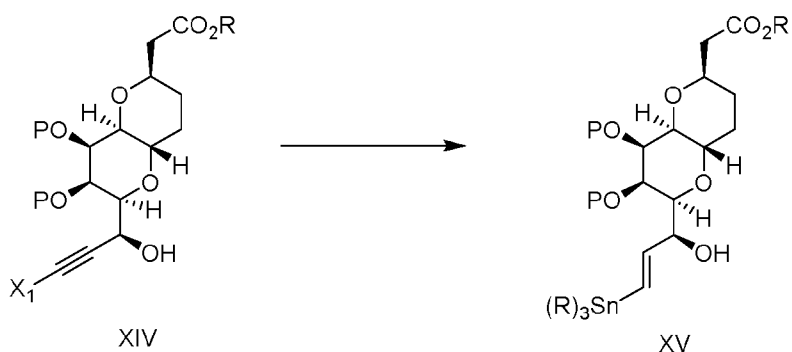
wherein R is C₁-C₈ alkyl group; R₁ is trialkyl silyl; P is an alcohol protected group;

(b) converting compound of formula XIII to compound of formula XIV;



wherein R is C₁-C₈ alkyl group, R₁ is trialkyl silyl, P is an alcohol protected group and X₁ is hydrogen or halogen;

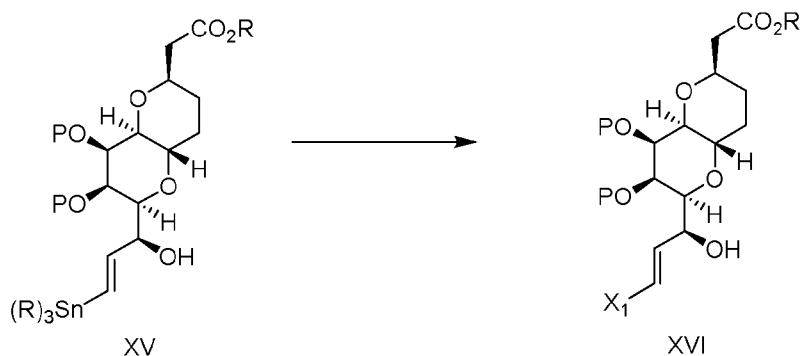
(c) treating compound of formula XIV with trialkyltin hydride to provide compound of formula XV;



wherein R is C₁-C₈ alkyl group, R₁ is trialkyl silyl, P is an alcohol protected group and X₁ is hydrogen or halogen;

(d) converting compound of formula XV to compound of formula XVI; and

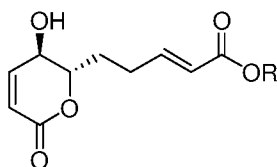
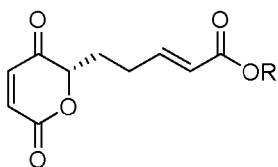
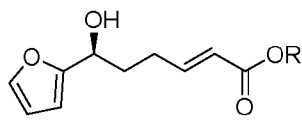
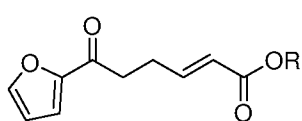
-8-



wherein R is C₁-C₈ alkyl group, P is an alcohol protected group and X₁ is hydrogen or halogen;

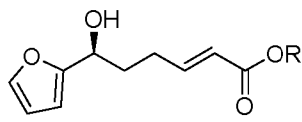
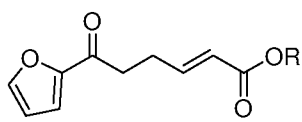
(e) protecting the compound of formula XVI to provide compound of formula II.

In the seventh embodiment, the present application provides a compound of formula IV or compound of formula V or isomers thereof or compound of formula VII or isomers thereof or compound of formula VIII or isomers thereof.

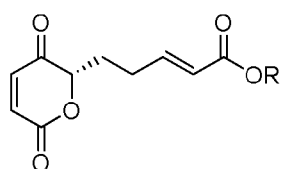


wherein R is C₁-C₈ alkyl group;

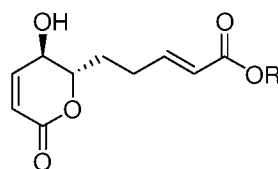
In the eighth embodiment, the present application provides a process for preparation of Eribulin or its pharmaceutically acceptable salts via compound of formula IV or compound of formula V or compound of formula VII or compound of formula VIII.



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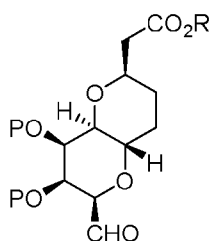
VII



VIII

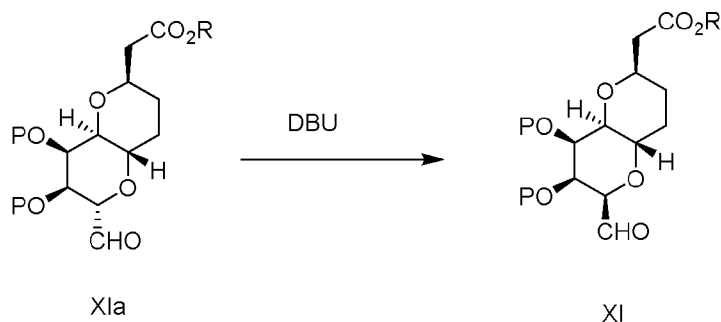
wherein R is C₁-C₈ alkyl group;

In the ninth embodiment, the present application provides an isomerization process for preparation of compound of formula XI



XI

wherein P is an alcohol protected group and R is C₁-C₈ alkyl group; which comprises: converting compound of formula XIa to compound of formula XI using 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and halogenated hydrocarbon solvent.



XIa

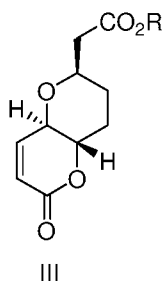
XI

wherein P is an alcohol protected group and R is C₁-C₈ alkyl group;

DETAILED DESCRIPTION

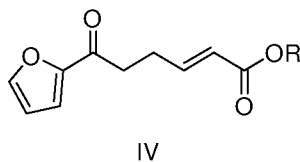
In the first embodiment, the present application provides a process for preparation of hexahydropyrano pyran compound of formula III,

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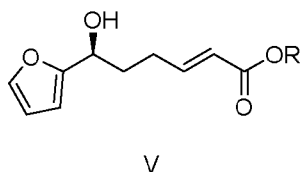
wherein R is C₁-C₈ alkyl group; which includes one or more of the following steps:

(a) converting furan or 2-acetyl furan to a compound of formula IV;



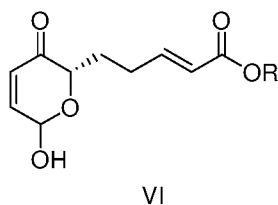
wherein R is C₁-C₈ alkyl group;

(b) reducing compound of formula IV to hydroxy compound of formula V;



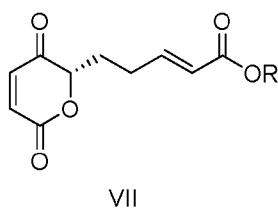
wherein R is C₁-C₈ alkyl group;

(c) converting hydroxy compound of formula V to pyran compound of formula VI;



wherein R is C₁-C₈ alkyl group;

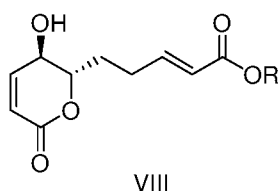
(d) oxidizing compound of formula VI to provide compound of formula VII;



wherein R is C₁-C₈ alkyl group;

(e) reducing the compound of formula VII to provide hydroxy compound of formula VIII; and

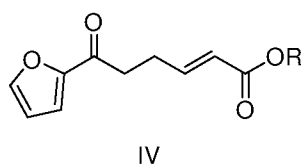
-11-



wherein R is C₁-C₈ alkyl group;

(f) converting hydroxy compound of formula VIII to hexahydropyrano pyran compound of formula III.

Step (a) involves converting furan or 2-acetyl furan to a compound of formula IV;



wherein R is C₁-C₈ alkyl group;

Step (a) may be carried out by reacting 2-acetyl furan with alkyl-4-halobut-2-enoate, or

by reacting 2-acetyl furan with alkyl-4-acetoxybut-2-enoate by employing pi-allyl mediated -Zn-enolate alkylation conditions, or

by reacting furan with (E)-6-alkoxy-6-oxohex-4-enoic acid by employing Friedel craft acylation conditions.

Suitable bases that may be used in step (a) include triethylamine, tributylamine, dibutylamine, morpholine, diethylamine, pyrrolidine and the like or any other suitable base known in the art.

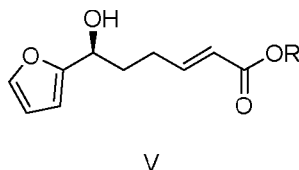
Suitable solvents that may be used in step (a) include ethers, aliphatic and alicyclic hydrocarbons, aromatic hydrocarbons, nitriles, polar aprotic solvents, nitromethane or mixtures thereof.

The reaction mixture obtained from step (a) may be optionally processed to remove any insoluble solids, and particles may be removed by methods such as decantation, centrifugation, gravity filtration, suction filtration, or any other techniques for the removal of solids. The product of step (a) may be isolated directly from the reaction mixture itself after the reaction is complete in step (a), or after conventional work up with techniques such as filtration, quenching with a suitable reagent, extraction, or the like. Optionally, the resulting product may be directly used for step

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(b) with or without isolation or it may be further purified, if isolated, to improve the purity of the product.

Step (b) involves reducing compound of formula IV to hydroxy compound of formula V;



wherein R is C₁-C₈ alkyl group;

Suitable catalysts that may be used in step (b) include, C₃-(S,S)-teth-TsDPEN RuCl], [Ru₂(p-PriC₆H₄Me)₂(μ-Cl)Cl]₂, N-[(1S,2S)-2-amino-1,2-diphenylethyl]-p-tolylsulphonamide; potassium tert-butyrate, hydrogen; trans-RuCl₂[(R)-xylbinap][(R)-daipen], [(η⁶-p-cymene)((1S,2S)-N-p-toluenesulfonyl-1,2-diphenylethylenediamine)] Ru], RuCl₂{(S)-2,2'-bis(di-4-tolylphosphanyl)-1,1'-binaphthyl}{(R)-2-dimethylamino-1-phenylethylamine}, (1S,2S)-N-p-toluenesulfonyl-1,2-diphenylethylenediamine-ruthenium(mesitylene), (R)-Ru(η⁶-mesitylene)-(S,S)-TsDPEN; sodium formate, N-hexadecyl-N,N,N-trimethylammonium bromide; potassium formate, RuCl(p-cymene)[(S,S)-Ts-DPEN], Cp*IrCl[(S,S)-MsDPEN], (S,S)-Noyori catalyst, L-Selectridereg, Rh[(((S,S)-BenzP*)(cod)]SbF₆; Ir-(S)-MeO-BIPHEP-BARF, (S)-RuCl[(1S,2S)-p-TsNCH(C₆H₅)CH(C₆H₅)NH₂](η⁶-mesitylene), RuCl(p-cymene) (1R2R)-N-(2,3,4,5,6-pentafluorobenzenesulfonyl)-1,2-diphenylethanediamine],

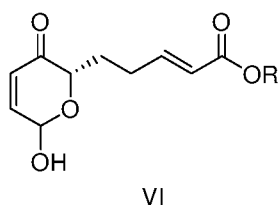
Step (b) may be carried out using (R)-2-Methyl-CBS-oxazaborolidine and borane-tetrahydrofuran or Borane-dimethyl sulfide and (1R,2S,3R,5R)-2-(1',3',2'-dioxaborolan-2'-yloxy)apopin-3-amine or (+)-B-Chlorodiisopinocampheylborane or any other suitable catalysts known in the art used for the selective reduction of ketones.

Step (b) may be carried out using enzymes like Glutamate dehydrogenase, Nicotinamide adenine dinucleotide, PRO-AKR, D-glucose, Saccharomyces cerevisiae (baker's yeast), [14C]-Sucrose and the like or combinations thereof or any other suitable enzymes known in the art.

Suitable solvents that may be used in step (b) include alcohols, ethers, aliphatic and alicyclic hydrocarbons, halogenated hydrocarbons, polar aprotic solvents or mixtures thereof.

The reaction mixture obtained from step (b) may be optionally processed to remove any insoluble solids, and particles may be removed by methods such as decantation, centrifugation, gravity filtration, suction filtration, or any other suitable techniques for the removal of solids. The product of step (b) may be isolated directly from the reaction mixture itself after the reaction is complete in step (b), or after conventional work up with techniques such as filtration, quenching with a suitable reagent, extraction, or the like. Optionally, the resulting product may be directly used for step (c) with or without isolation or it may be further purified, if isolated, to improve the purity of the product.

Step (c) involves converting hydroxy compound of formula V to pyran compound of formula VI;



wherein R is C₁-C₈ alkyl group;

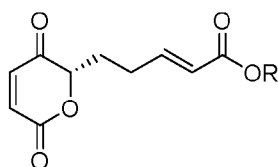
Step (c) may be carried out by employing the Achmatowicz reaction conditions or using VO (acac)₂ or H₂O₂ or any other conditions known in the art.

Suitable solvents that may be used in step (c) include alcohols, ethers, aliphatic and alicyclic hydrocarbons, halogenated hydrocarbons, polar aprotic solvents or mixtures thereof.

The reaction mixture obtained from step (c) may be optionally processed to remove any insoluble solids, and particles may be removed by methods such as decantation, centrifugation, gravity filtration, suction filtration, or any other suitable techniques for the removal of solids. The product of step (c) may be isolated directly from the reaction mixture itself after the reaction is complete in step (c), or after conventional work up with techniques such as filtration, quenching with a suitable reagent, extraction, or the like. Optionally, the resulting product may be directly used for step (d) with or without isolation or it may be further purified, if isolated, to improve the purity of the product.

Step (d) involves oxidizing compound of formula VI to provide compound of formula VII;

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VII

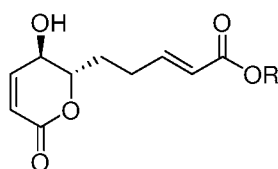
wherein R is C₁-C₈ alkyl group;

Suitable reagents that may be used in step (d) include chromium trioxide in dilute sulfuric acid (Jones reagent), complex of chromium(VI) oxide with pyridine (Collins reagent), pyridinium chlorochromate (PCC), Dess–Martin periodinane (DMP), potassium dichromate, oxalyl chloride & dimethylsulfoxide and the like or any other suitable reagents that are known in the art.

Suitable solvents that may be used in step (d) include ethers, aliphatic and alicyclic hydrocarbons, halogenated hydrocarbons, polar aprotic solvents or mixtures thereof.

The reaction mixture obtained from step (d) may be optionally processed to remove any insoluble solids, and particles may be removed by methods such as decantation, centrifugation, gravity filtration, suction filtration, or any other suitable techniques for the removal of solids. The product of step (d) may be isolated directly from the reaction mixture itself after the reaction is complete in step (d), or after conventional work up with techniques such as filtration, quenching with a suitable reagent, extraction, or the like. Optionally, the resulting product may be directly used for step (e) with or without isolation or it may be further purified, if isolated, to improve the purity of the product.

Step (e) involves reducing the compound of formula VII to provide hydroxy compound of formula VIII; and



VIII

wherein R is C₁-C₈ alkyl group;

Suitable reagents that may be used in step (e) include sodium borohydride, lithium aluminum hydride, sodium trimethoxy borohydride, Lithium borohydride, acetoxyborohydride or the like; or in combination with zinc chloride or cerium chloride and the like or any other suitable reducing agent known in the art.

Suitable solvents that may be used in step (e) include water, ethers, alcohols, halogenated hydrocarbons, aromatic hydrocarbons or mixtures thereof.

The reaction mixture obtained from step (e) may be optionally processed to remove any insoluble solids, and particles may be removed by methods such as decantation, centrifugation, gravity filtration, suction filtration, or any other suitable techniques for the removal of solids. The product of step (e) may be isolated directly from the reaction mixture itself after the reaction is complete in step (e), or after conventional work up with techniques such as filtration, quenching with a suitable reagent, extraction, or the like. Optionally, the resulting product may be directly used for step (f) with or without isolation or it may be further purified, if isolated, to improve the purity of the product.

Step (f) involves converting hydroxy compound of formula VIII to hexahydropyrano pyran compound of formula III.

Suitable solvents that may be used in step (f) include ethers, alcohols, halogenated hydrocarbons, aromatic hydrocarbons polar aprotic solvents or mixtures thereof.

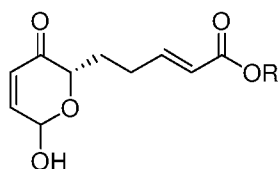
The reaction mixture obtained from step (f) may be optionally processed to remove any insoluble solids, and particles may be removed by methods such as decantation, centrifugation, gravity filtration, suction filtration, or any other suitable techniques for the removal of solids. The product of step (f) may be isolated directly from the reaction mixture itself after the reaction is complete in step (f), or after conventional work up with techniques such as filtration, quenching with a suitable reagent, extraction, or the like. Optionally, the resulting product may be directly used for next step with or without isolation or it may be further purified, if isolated, to improve the purity of the product.

Compound of formula III may be further converted to compound of formula II by following the procedures known in the art or the processes described herein.

Compound of formula III may be further converted to eribulin or its pharmaceutically acceptable salts by following the procedures known in the art.

In the second embodiment, the present application provides a process for preparation of pyran compound of formula VI,

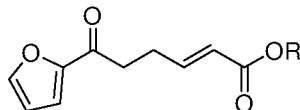
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VI

wherein R is C₁-C₈ alkyl group; which comprises:

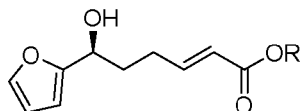
(a) converting furan or 2-acetyl furan to a compound of formula IV;



IV

wherein R is C₁-C₈ alkyl group;

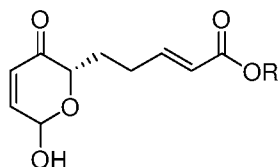
(b) reducing compound of formula IV to hydroxy compound of formula V;



V

wherein R is C₁-C₈ alkyl group;

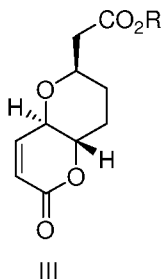
(c) converting hydroxy compound of formula V to pyran compound of formula VI;



VI

wherein R is C₁-C₈ alkyl group.

In the third embodiment, the present application provides a process for preparation of compound of formula III comprising:

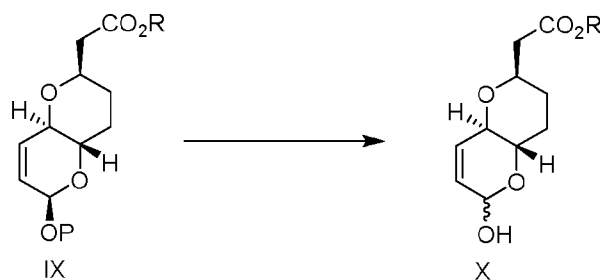


III

wherein R is C₁-C₈ alkyl group;

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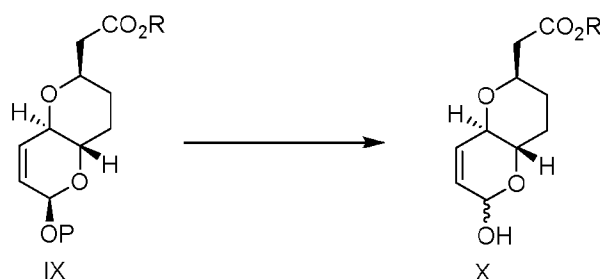
(a) deprotecting compound of formula IX to provide compound of formula X;



wherein R is C₁-C₈ alkyl group, P is an alcohol protected group;

(b) oxidizing compound of formula X to provide compound of formula III.

Step (a) involves deprotecting compound of formula IX to provide compound of formula X;



wherein R is C₁-C₈ alkyl group, P is an alcohol protected group;

Suitable reagents that may be used in step (a) include resins such as Amberlite® IRA-400 chloride form, Amberlite® IRA910 chloride form, Ambersep® 900 hydroxide form, Amberlite® IRA-410 chloride form, Amberlite® IRA402 chloride form, Amberlite® IRA404 chloride form, Amberlite® IRN78 hydroxide form, Amberlyst® A26 hydroxide form and the like or bases such as triethylamine and the like or any other suitable reagents known in the art.

Suitable solvents that may be used in step (a) include water, alcohols, ketones, ethers, aliphatic and alicyclic hydrocarbons, halogenated hydrocarbons, aromatic hydrocarbons, nitriles, polar aprotic solvents, nitromethane and mixtures thereof.

The reaction mixture obtained from step (a) may be optionally processed to remove any insoluble solids, and particles may be removed by methods such as decantation, centrifugation, gravity filtration, suction filtration, or any other techniques for the removal of solids. The product of step (a) may be isolated directly from the reaction mixture itself after the reaction is complete in step (a), or after conventional work up with techniques such as filtration, quenching with a suitable reagent, extraction, or the like. Optionally, the resulting product may be directly used for step

(b) with or without isolation or it may be further purified, if isolated, to improve the purity of the product.

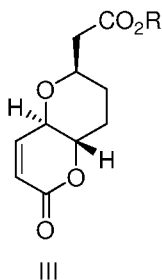
Step (b) involves oxidizing compound of formula X to provide compound of formula III.

Suitable reagents that may be used in step (b) include chromium trioxide in dilute sulfuric acid (Jones reagent), complex of chromium(VI) oxide with pyridine (Collins reagent), pyridinium chlorochromate (PCC), Dess–Martin periodinane (DMP), potassium dichromate, oxalyl chloride & dimethylsulfoxide and the like or any other suitable reagents that are known in the art.

Suitable solvents that may be used in step (b) include ethers, aliphatic and alicyclic hydrocarbons, halogenated hydrocarbons, polar aprotic solvents or mixtures thereof.

The reaction mixture obtained from step (b) may be optionally processed to remove any insoluble solids, and particles may be removed by methods such as decantation, centrifugation, gravity filtration, suction filtration, or any other suitable techniques for the removal of solids. The product of step (b) may be isolated directly from the reaction mixture itself after the reaction is complete in step (b), or after conventional work up with techniques such as filtration, quenching with a suitable reagent, extraction, or the like. Optionally, the resulting product may be directly used for next step with or without isolation or it may be further purified, if isolated, to improve the purity of the product.

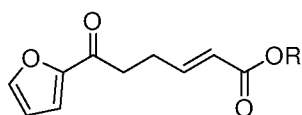
In the fourth embodiment, the present application provides a process for preparation of compound of formula III,



wherein R is C₁-C₈ alkyl group; which comprises:

(a) converting furan or 2-acetyl furan to a compound of formula IV;

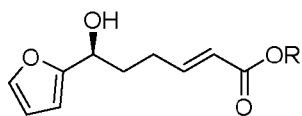
-19-



IV

wherein R is C₁-C₈ alkyl group;

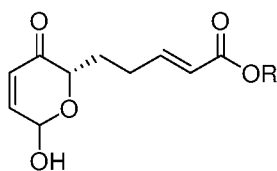
(b) reducing compound of formula IV to hydroxy compound of formula V;



V

wherein R is C₁-C₈ alkyl group;

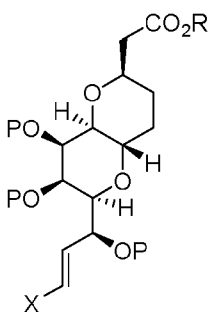
(c) converting hydroxy compound of formula V to pyran compound of formula VI;



VI

wherein R is C₁-C₈ alkyl group.

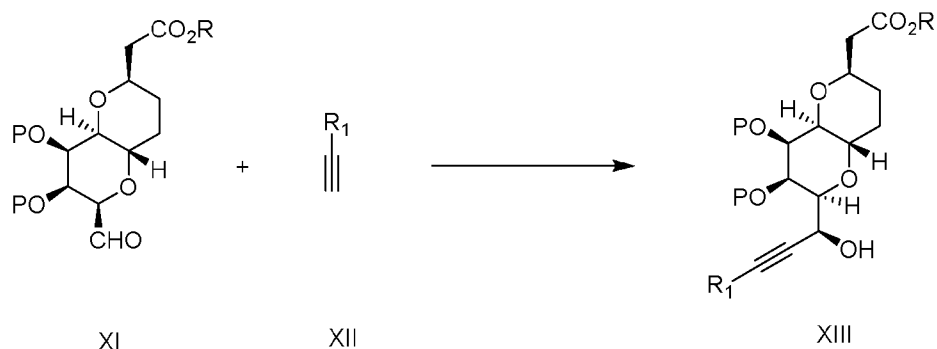
In the fifth embodiment, the present application provides a process for preparation of octahydropyrano [3, 2-b] pyran compound of formula II,



II

wherein P is an alcohol protected group, X is a halogen and R is C₁-C₈ alkyl group;
which comprises: treating aldehyde compound of formula XI with compound of formula XII to provide compound of formula XIII;

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wherein R is C₁-C₈ alkyl group, R₁ is trialkyl silyl and P is an alcohol protected group.

Suitable catalysts that may be used for preparation of compound of formula III include dimethyl aluminium chloride, diethyl aluminium chloride, chromium dichloride, nickel dichloride, zirconocene dichloride and the like or mixtures thereof or any other catalyst known in the art used for alkyne addition on aldehydes.

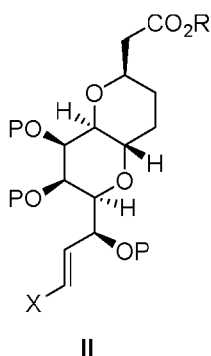
Suitable bases that may be used for preparation of compound of formula III include *n*-Butyllithium, *sec*-Butyllithium, *tert*-Butyllithium, lithium bis(trimethylsilyl)amide, lithium diisopropylamide and the like or any other suitable reagents known in the art.

Suitable solvents that may be used for preparation of compound of formula III include ethers, aliphatic and alicyclic hydrocarbons, halogenated hydrocarbons, polar aprotic solvents or mixtures thereof.

The reaction mixture obtained after completion of alkyne addition on aldehydes may be optionally processed to remove any insoluble solids, and particles may be removed by methods such as decantation, centrifugation, gravity filtration, suction filtration, or any other suitable techniques for the removal of solids. The product may be isolated directly from the reaction mixture itself after the reaction is complete or after conventional work up with techniques such as filtration, quenching with a suitable reagent, extraction, or the like. Optionally, the resulting product may be directly used for next step with or without isolation or it may be further purified, if isolated, to improve the purity of the product.

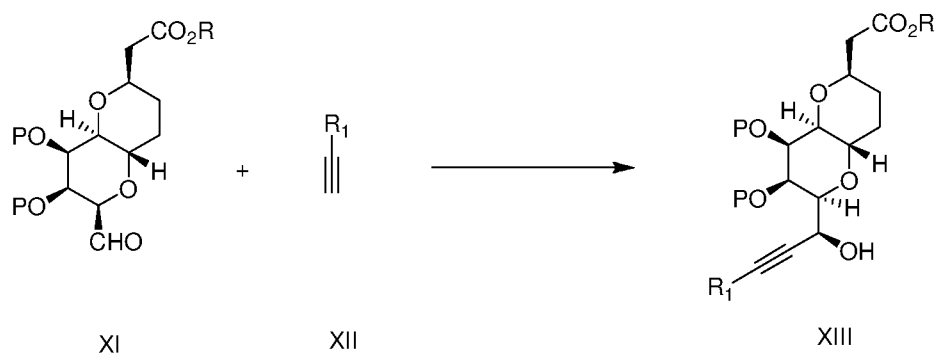
In the sixth embodiment, the present application provides a process for preparation of octahydropyrano [3, 2-b] pyran compound of formula (II),

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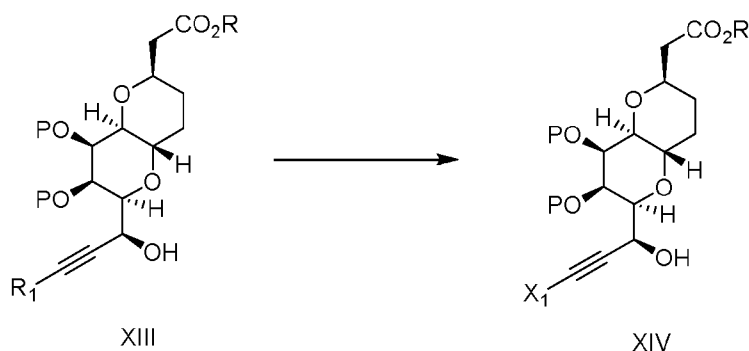
wherein R is C₁-C₈ alkyl group, P is alcohol protecting group and X is a halogen; which includes one or more of the following steps:

(a) treating aldehyde compound of formula XI with compound of formula XII to provide compound of formula XIII;



wherein R is C₁-C₈ alkyl group; R₁ is trialkyl silyl; P is an alcohol protected group;

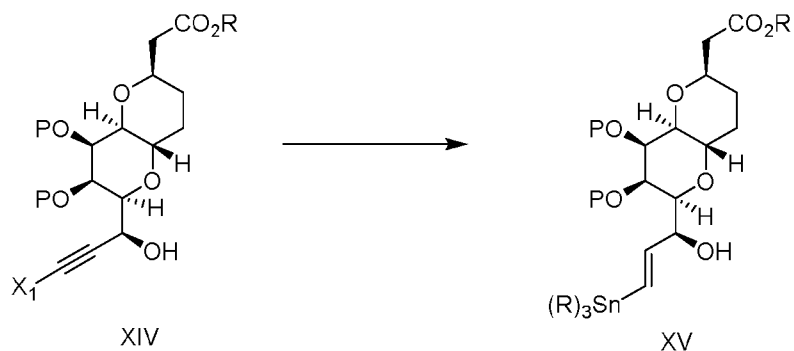
(b) converting compound of formula XIII to compound of formula XIV;



wherein R is C₁-C₈ alkyl group, R₁ is trialkyl silyl, P is an alcohol protected group and X₁ is hydrogen or halogen;

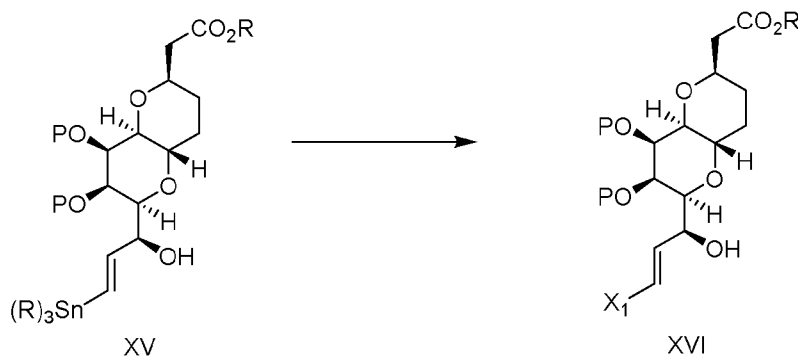
(c) treating compound of formula XIV with trialkyltin hydride to provide compound of formula XV;

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wherein R is C₁-C₈ alkyl group, R₁ is trialkyl silyl, P is an alcohol protected group and X₁ is hydrogen or halogen;

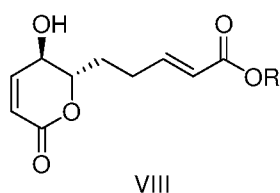
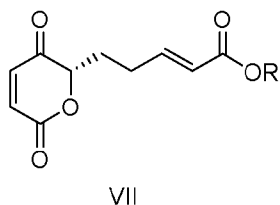
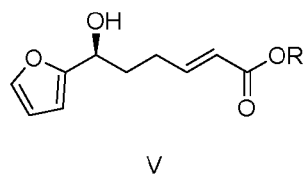
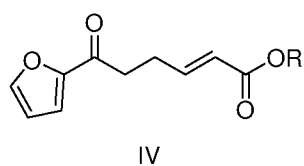
(d) converting compound of formula XV to compound of formula XVI; and



wherein R is C₁-C₈ alkyl group, P is an alcohol protected group and X₁ is hydrogen or halogen;

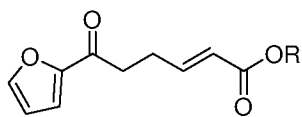
(e) protecting the compound of formula XVI to provide compound of formula II.

In the seventh embodiment, the present application provides a compound of formula IV or compound of formula V or isomers thereof or compound of formula VII or isomers thereof or compound of formula VIII or isomers thereof.

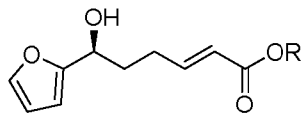


wherein R is C₁-C₈ alkyl group;

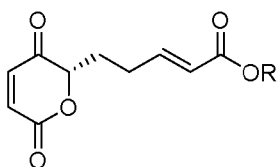
In the eighth embodiment, the present application provides a process for preparation of Eribulin or its pharmaceutically acceptable salts via compound of formula IV or compound of formula V or compound of formula VII or compound of formula VIII.



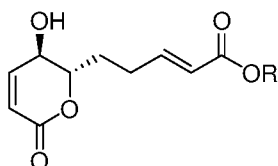
IV



V



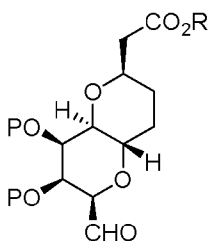
VII



VIII

wherein R is C₁-C₈ alkyl group;

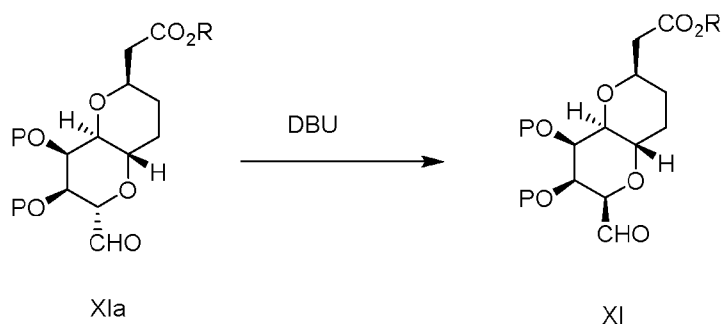
In the ninth embodiment, the present application provides an isomerization process for preparation of compound of formula XI



XI

wherein P is an alcohol protected group and R is C₁-C₈ alkyl group; which comprises: converting compound of formula XIa to compound of formula XI using 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) and halogenated hydrocarbon solvent.

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wherein P is an alcohol protected group and R is C₁-C₈ alkyl group;

DEFINITIONS

The following definitions are used in connection with the present application unless the context indicates otherwise. In general, the number of carbon atoms present in a given group or compound is designated "C_x-C_y", where x and y are the lower and upper limits, respectively. For example, a group designated as "C₁-C₆" contains from 1 to 6 carbon atoms. The carbon number as used in the definitions herein refers to carbon backbone and carbon branching, but does not include carbon atoms of the substituents, such as alkoxy substitutions or the like.

As used herein, "an alcohol protecting group" is a functional group that protects the alcohol group from participating in reactions that are occurring in other parts of the molecule. Suitable alcohol protecting groups that are used in the present application include, acetyl, benzoyl, benzyl, β-methoxyethoxymethyl ether, methoxymethyl ether, dimethoxytrityl, *p*-methoxybenzyl ether, methylthiomethyl ether, allyl ether, *t*-butyl ether, pivaloyl, trityl, silyl ether (e.g., trimethylsilyl (TMS), *t*-butyldimethylsilyl (TBMDS), *t*-butyldiphenylsilyl (TBDPS), *t*-butyldimethylsilyloxymethyl (TOM) or triisopropylsilyl (TIPS) ether), tetrahydropyranyl (THP), methyl ether and ethoxyethyl ether (EE) or any suitable alcohol protecting group known in the art used for protecting alcohols.

An "alcohol" is an organic compound containing a carbon bound to a hydroxyl group. "C₁-C₆ alcohols" include methanol, ethanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, hexafluoroisopropyl alcohol, ethylene glycol, 1-propanol, 2-propanol (isopropyl alcohol), 2-methoxyethanol, 1-butanol, 2-butanol, *i*-butyl alcohol, *t*-butyl alcohol, 2-ethoxyethanol, diethylene glycol, 1-, 2-, or 3-pentanol, neo-pentyl alcohol, *t*-pentyl alcohol, diethylene glycol monomethyl ether, diethylene glycol monoethyl ether, cyclohexanol, phenol, glycerol and the like.

An "aliphatic hydrocarbon" is a liquid hydrocarbon compound, which may be linear, branched, or cyclic and may be saturated or have as many as two double bonds. A liquid hydrocarbon compound that contains a six-carbon group having three double bonds in a ring is called "aromatic." Examples of "C₅-C₈ aliphatic or aromatic hydrocarbons" include *n*-pentane, isopentane, neopentane, *n*-hexane, isohexane, 3-methylpentane, 2,3-dimethylbutane, neohexane, *n*-heptane, isoheptane, 3-methylhexane, neoheptane, 2,3-dimethylpentane, 2,4-dimethylpentane, 3,3-dimethylpentane, 3-ethylpentane, 2,2,3-trimethylbutane, *n*-octane, isooctane, 3-methylheptane, neooctane, cyclohexane, methylcyclohexane, cycloheptane, petroleum ethers, benzene toluene, ethylbenzene, *m*-xylene, *o*-xylene, *p*-xylene, trimethylbenzene, chlorobenzene, fluorobenzene, trifluorotoluene, anisole, and the like.

An "aromatic hydrocarbon solvent" refers to a liquid, unsaturated, cyclic, hydrocarbon containing one or more rings which has delocalized conjugated π system. Examples of an aromatic hydrocarbon solvent include benzene toluene, ethylbenzene, *m*-xylene, *o*-xylene, *p*-xylene, indane, naphthalene, tetralin, trimethylbenzene, chlorobenzene, fluorobenzene, trifluorotoluene, anisole, C₆-C₁₂ aromatic hydrocarbons and the like.

An "ester" is an organic compound containing a carboxyl group -(C=O)-O- bonded to two other carbon atoms. "C₃-C₆ esters" include ethyl acetate, *n*-propyl acetate, *n*-butyl acetate, isobutyl acetate, *t*-butyl acetate, ethyl formate, methyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate and the like.

An "ether" is an organic compound containing an oxygen atom -O- bonded to two other carbon atoms. "C₂-C₆ ethers" include diethyl ether, diisopropyl ether, methyl *t*-butyl ether, glyme, diglyme, tetrahydrofuran, 2-methyltetrahydrofuran, 1, 4-dioxane, dibutyl ether, dimethylfuran, 2-methoxyethanol, 2-ethoxyethanol, anisole and the like.

A "halogenated hydrocarbon" is an organic compound containing a carbon bound to a halogen. Halogenated hydrocarbons include dichloromethane, 1,2-dichloroethane, trichloroethylene, perchloroethylene, 1,1,1-trichloroethane, 1,1,2-trichloroethane, chloroform, carbon tetrachloride and the like.

A "ketone" is an organic compound containing a carbonyl group -(C=O)- bonded to two other carbon atoms. "C₃-C₆ ketones" include acetone, ethyl methyl ketone, diethyl ketone, methyl isobutyl ketone, ketones and the like.

A “nitrile” is an organic compound containing a cyano $-(C\equiv N)$ bonded to another carbon atom. “C₂-C₆ Nitriles” include acetonitrile, propionitrile, butanenitrile and the like.

A “polar aprotic solvents” include *N,N*-dimethylformamide, *N,N*-dimethylacetamide, dimethylsulfoxide, sulfolane, *N*-methylpyrrolidone and the like;

Certain specific aspects and embodiments of the present application will be explained in greater detail with reference to the following examples, which are provided only for purposes of illustration and should not be construed as limiting the scope of the application in any manner. Reasonable variations of the described procedures are intended to be within the scope of the present application. While particular aspects of the present application have been illustrated and described, it would be obvious to those skilled in the art that various other changes and modifications can be made without departing from the spirit and scope of the invention. It is therefore intended to cover in the appended claims all such changes and modifications that are within the scope of this application.

EXAMPLES

EXAMPLE 1: Preparation of methyl (E)-6-(furan-2-yl)-6-oxohex-2-enoate.

Titanium tetrachloride (18 mL) was slowly added to the reaction mass containing 2-acetyl furan (50 g), toluene (1000 mL) and diethylamine (210 g) at 0 °C. The resultant reaction mixture was stirred at 0 °C for 3 hours and further stirred at 27 °C for 20 hours. The obtained reaction mass was filtered, washed with toluene (500 mL) and filtrate was distilled completely at 40 °C under reduced pressure. Dimethylformamide (250 mL), molecular sieves (50 g) and methyl 4-bromocrotonate (50 g) were added to the compound at 27 °C. Reaction mixture heated to 45 °C and stirred at 45 °C for 20 hours. Water (500 mL) and ethyl acetate (500 mL) was added to the reaction mass at 25 °C and stirred for 15 minutes. Layers were separated and aqueous layer extracted with ethyl acetate (500 mL). Combined organic layer washed with water (250 mL), brine solution (250 mL) and dried with anhydrous sodium sulfate (25 g). The organic layer was concentrated *in vacuo*, the obtained crude product was purified by using column chromatography (eluent: EtOAc/hexane) to afford the titled product.

EXAMPLE 2: Preparation of methyl (E)-6-(furan-2-yl)-6-oxohex-2-enoate.

Boron trifluoride diethyl etherate (0.2 mL) was slowly added to the reaction mass

containing furan (1.7 g), methyl (E)-5-hydroxypent-2-enoate (3.0 g), trifluoroacetic anhydride (4.8 g) and toluene (30 mL) at 28 °C. The resultant reaction mixture was heated to 50 °C and stirred at 50 °C for 2 hours. Aqueous sodium bicarbonate solution (30 mL) was added to the reaction mass at 5 °C and stirred for 10 minutes. Layers were separated and aqueous layer extracted with toluene (30 mL). Combined organic layer washed with water (15 mL) and dried with anhydrous sodium sulfate (0.6 g). The organic layer was concentrated *in vacuo* to afford the titled product (3.9 g).

EXAMPLE 3: Preparation of methyl (S,E)-6-(furan-2-yl)-6-hydroxyhex-2-enoate. Triethylamine (7.1 mL) was slowly added to the Formic acid (17.8 mL) under argon atmosphere at 28 °C and stirred for 10 minutes. Methyl (E)-6-(furan-2-yl)-6-oxohex-2-enoate (10 g) added to the reaction mixture at 30 °C and the resultant reaction mixture was bubbled with argon for 2 hours at 28 °C. C3-[(S,S)-teth-TsDpen RuCl] (297 mg) was added to the reaction mass under argon atmosphere at 28 °C. Reaction mixture heated to 62 °C and stirred at 62 °C for 3 hours 30 minutes. Water (150 mL) was added to the reaction mass and the reaction mass was extracted with ethyl acetate (200 mL + 100 mL). Combined organic layer was washed with sodium bicarbonate solution (2x100 mL), water (100 mL) and 20% brine solution (100 mL). The organic layer was concentrated *in vacuo* to afford the titled product.

EXAMPLE 4: Preparation of (6S)-6-((E)-5-methoxy-5-oxopent-3-en-1-yl)-5-oxo-5,6-dihydro-2H-pyran-2-yl benzoate: Sodium acetate Trihydrate (16.2 g) and sodium bicarbonate (20 g) were charged in to the reaction mass containing (S,E)-6-(furan-2-yl)-6-hydroxyhex-2-enoate (25 g) tetrahydrofuran (250 mL) and water (125 mL) at 0 °C. N-Bromosuccinimide (22.2 g) was slowly added to the reaction mass at 1 °C and the resultant reaction mixture was stirred at 27 °C for 1 hour. Water (125 mL) and dichloromethane (250 mL) was added to the reaction mass at 28 °C and stirred for 20 minutes. Layers were separated and aqueous layer extracted with dichloromethane (125 mL). Combined organic layer washed with water (3x250 mL) and dried with anhydrous sodium sulfate (6.2 g).

Triethylamine (16.6 mL) and 4-Dimethylaminopyridine (0.025 g) were added to the organic layer at -71 °C. Benzoyl chloride was slowly added to the reaction mixture at -70 °C and the resultant reaction mixture was stirred at -70 °C for 3 hours. Water (125 mL) was added to the reaction mixture at 10 °C and stirred for 50 minutes. Layers were separated, aqueous layer extracted with dichloromethane (125 mL) and the combined organic layer washed with water (3x250 mL). Charcoal (2.5 g) was

added to the organic layer and stirred for 1 hour. Filtered the organic layer through Celite bed, washed the bed with dichloromethane (50 mL). Filtrate dried with anhydrous sodium sulfate (5 g) and concentrated *in vacuo*. Methyl tert-butyl ether (25 mL) was added to the crude compound and distilled completely at 40 °C. Methyl tert-butyl ether (30 mL) was added to the crude compound at 30 °C and cooled to 0 °C. Separated solid was filtered, washed with Methyl tert-butyl ether (25 mL) and dried to afford title compound (12.7 g).

EXAMPLE 5: Preparation of (2S,5R,6S)-5-hydroxy-6-((E)-5-methoxy-5-oxopent-3-en-1-yl)-5,6-dihydro-2H-pyran-2-yl benzoate: Cerium (III) chloride heptahydrate (141.6 g) was added to the reaction mass containing (6S)-6-((E)-5-methoxy-5-oxopent-3-en-1-yl)-5-oxo-5,6-dihydro-2H-pyran-2-yl benzoate (100 g) and dichloromethane (2000 mL), methanol (1500 mL) at -75 °C and stirred at -75 °C for 30 minutes. Sodium borohydride (14.4 g) was added to the reaction mass at -75 °C and the resultant reaction mixture was stirred at -75 °C for 1 hour 10 minutes. Water (100 mL) was added slowly to the reaction mass at -50 °C and stirred for 1 hour 20 minutes. Reaction mass filtered through Celite bed and Celite bed was washed with dichloromethane (500 mL). Filtrate layers were separated, organic layer washed with water (2x1000 mL) and dried with anhydrous sodium sulfate (25 g). The organic layer was concentrated *in vacuo* and the obtained crude compound was triturated with hexane (2x300 mL) to afford the titled product (74 g).

EXAMPLE 6: Preparation of (2S,4aR,6R,8aS)-6-(2-methoxy-2-oxoethyl)-2,4a,6,7,8,8a-hexahydropyrano[3,2-b]pyran-2-yl benzoate: Tetra-n-butylammonium fluoride (1M in THF, 54 mL) solution was slowly added to the reaction mass containing (2S,5R,6S)-5-hydroxy-6-((E)-5-methoxy-5-oxopent-3-en-1-yl)-5,6-dihydro-2H-pyran-2-yl benzoate (9 g) and tetrahydrofuran (450 mL) at 28 °C under nitrogen atmosphere. The resultant reaction mixture was stirred at 28 °C for 3 hours. Water (180 mL) was added to the reaction mass and the reaction mass was extracted with ethyl acetate (2x180 mL). Combined organic layer was washed with sodium bicarbonate solution (3x180 mL), water (180 mL), 20% brine solution (180 mL) and dried with anhydrous sodium sulfate (18 g). The organic layer was concentrated *in vacuo*, the obtained crude product was chased with hexane (2x 45 mL). Hexane (90 mL) was added to the crude compound and the resultant reaction mixture was stirred at 3 °C for 1 hour. Separated solid was filtered and dried to afford the titled product (7.3 g).

EXAMPLE 7: Preparation of (2S,4aR,6R,8aS)-6-(2-methoxy-2-oxoethyl)-2,4a,6,7,8,8a-hexahydropyrano[3,2-b]pyran-2-yl benzoate: Cerium (III) chloride heptahydrate (10.1 g) was added to the reaction mass containing (6S)-6-((E)-5-methoxy-5-oxopent-3-en-1-yl)-5-oxo-5,6-dihydro-2H-pyran-2-yl benzoate (9 g) and methyl tert-butyl ether (135 mL), methanol (90 mL) at -70 °C and stirred at -70 °C for 15 minutes. Sodium borohydride (1.03 g) was added to the reaction mass at -71 °C and the resultant reaction mixture was stirred at -70 °C for 1 hour 30 minutes. Water (90 mL) was added slowly to the reaction mass at -10 °C. Reaction mass was extracted with ethyl acetate (2x180 mL), combined organic layer washed with water (3x90 mL), brine solution (90 mL) and dried with anhydrous sodium sulfate. The organic layer was concentrated *in vacuo* and chased with tetrahydrofuran (2x45 mL).

The obtained compound was dissolved in tetrahydrofuran (450 mL). Tetra-n-butylammonium fluoride (1M in THF, 54 mL) solution was slowly added to the reaction mass at 28 °C under nitrogen atmosphere and the resultant reaction mixture was stirred at 28 °C for 3 hours. Water (180 mL) was added to the reaction mass and the reaction mass was extracted with ethyl acetate (2x180 mL). Combined organic layer was washed with sodium bicarbonate solution (3x180 mL), water (180 mL), 20% brine solution (180 mL) and dried with anhydrous sodium sulfate (18 g). The organic layer was concentrated *in vacuo*, the obtained crude product was chased with hexane (2x 45 mL). Hexane (90 mL) was added to the crude compound and the resultant reaction mixture was stirred at 3 °C for 1 hour. Separated solid was filtered and dried to afford the titled product (7.3 g).

EXAMPLE 8: Preparation of methyl 2-((2R,4aS,8aR)-6-oxo-2,3,4,4a,6,8a-hexahydropyrano[3,2-b]pyran-2-yl)acetate: (2S,4aR,6R,8aS)-6-(2-methoxy-2-oxoethyl)-2,4a,6,7,8,8a-hexahydropyrano[3,2-b]pyran-2-yl benzoate (1.0g), methanol (20 mL), water (1.8 mL) and Amberlite IRA 400 Cl form (0.1 g) charged into a round bottom flask. The resultant reaction mixture was heated to 63 °C and stirred at 63°C for 3 hours 30 minutes. Reaction mass was concentrated *in vacuo* and chased with acetone (10 mL). The resultant crude compound was dissolved in acetone (20 mL). Solution of chromium trioxide in dilute sulfuric acid (Jones reagent; 3.0 mL) was added to the reaction mass at 2 °C and stirred at 2 °C for 5 hours. Isopropyl alcohol (0.5 mL) was added to the reaction mass and the resultant reaction mass was filtered through Celite bed and washed with dichloromethane (10 mL). Filtrate concentrated *in vacuo* and the obtained crude compound was dissolved in dichloromethane (20 mL). Organic

layer was washed with water (10 mL), saturated sodium bicarbonate solution (2x10 mL) and dried with anhydrous sodium sulfate (0.5 g). The organic layer was concentrated *in vacuo*, the obtained crude product was purified by using column chromatography (eluent: EtOAc/hexane) to afford the titled product (500 mg).

EXAMPLE 9: Preparation of methyl (E)-5-((2S,3R)-3-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)pent-2-enoate: Jones reagent (prepared using 45 g of chromium trioxide, 38.9 mL of sulfuric acid and 108 mL of water) was slowly added to the reaction mass containing methyl (E)-5-((2S)-6-hydroxy-3-oxo-3,6-dihydro-2H-pyran-2-yl)pent-2-enoate (90 g), dichloromethane (1050 mL) and acetone (900 mL) at 0 °C and stirred at 0 °C for 1 hour. Isopropyl alcohol (31.5 mL) was slowly added to the reaction mass at 4 °C and stirred at 4 °C for 10 minutes. Dichloromethane (450 mL) was added to the reaction mass at 4 °C and stirred at 4 °C for 15 minutes. Reaction mass filtered through Celite bed and bed washed with dichloromethane (450 mL). Filtrate was concentrated *in vacuo* up to about 70 % of reaction mass volume. Reaction mass was chased with dichloromethane (450 mL) up to 70 % of reaction mass volume. The resultant compound (methyl (S,E)-5-(3,6-dioxo-3,6-dihydro-2H-pyran-2-yl)pent-2-enoate) was dissolved in dichloromethane (900 mL), organic layer was washed with water (4x900 mL) and dried with anhydrous sodium sulfate (18 g).

Zinc chloride solution (0.05M in THF; 121.6 g) was added to the organic layer at -75 °C and stirred at -70 °C for 30 minutes. Sodium borohydride (16.2 g) was added to the reaction mass in lot wise (four lots) at -70 °C and the resultant reaction mixture was stirred at -70 °C for 4 hours. Water (80 mL) was added slowly to the reaction mass at -70 °C and stirred for 30 minutes. Dichloromethane (400 mL) and water (320 mL) was added to the reaction mass and stirred for 15 minutes. Reaction mass filtered through Celite bed and Celite bed was washed with dichloromethane (400 mL). Filtrate layers were separated, organic layer washed with water (400 mL) and dried with anhydrous sodium sulfate (16 g). The organic layer was concentrated *in vacuo*, the obtained crude product was purified by using column chromatography (eluent: EtOAc/hexane) to afford the titled product.

EXAMPLE 10: Preparation of methyl 2-((2R,4aS,8aR)-6-oxo-2,3,4,4a,6,8a-hexahydropyrano[3,2-b]pyran-2-yl)acetate: Tetra-n-butylammonium fluoride (1M in THF, 46.1 g) solution was slowly added to the reaction mass containing methyl (E)-5-((2S,3R)-3-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)pent-2-enoate (40 g), toluene (4000 mL) and molecular sieves (16 g) at 28 °C under nitrogen atmosphere and the

resultant reaction mixture was stirred at 28 °C for 3 hours. Reaction mass was filtered and washed with toluene and the resultant reaction mass was directly loaded in to column and purified to afford title compound (16.5 g) as 70:30 ratio of desired and undesired isomers. The diastereomers are further purified using column chromatography (eluent: IPA/hexane) to afford the titled product.

EXAMPLE 11: Preparation of methyl 2-((2R,4aS,7S,8R,8aR)-7,8-dihydroxy-6-oxooctahydropyrano[3,2-b]pyran-2-yl)acetate: N-Methylmorpholine-N-Oxide (7.8 g) was added to the reaction mass containing methyl 2-((2R,4aS,8aR)-6-oxo-2,3,4,4a,6,8a-hexahydropyrano[3,2-b]pyran-2-yl)acetate (10 g) and acetone (200 mL) at 0 °C and stirred for 10 minutes. Potassium osmate dihydrate (0.325 g) dissolved in water (7.95 mL) and the obtained solution was slowly added to the reaction mass at 2 °C and stirred at 2 °C for 15 minutes. The resultant reaction mass was stirred at 26 °C for 4 hours 30 minutes. Sodium sulfite (10 g) was added to the reaction mass and stirred for 1 hour. Reaction mass filtered through Celite bed and bed washed with acetone (200 mL). Filtrate layers were separated and organic layer dried with anhydrous sodium sulfate (40 g). The organic layer was concentrated *in vacuo* to afford the titled product or the organic layer containing the compound is used in next stage.

EXAMPLE 12: Preparation of methyl 2-((2R,4aS,7S,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-oxooctahydropyrano[3,2-b]pyran-2-yl)acetate: Imidazole (26.3 g) was added to the reaction mass containing methyl 2-((2R,4aS,7S,8R,8aR)-7,8-dihydroxy-6-oxooctahydropyrano[3,2-b]pyran-2-yl) acetate (17.2 g; crude) and dimethylformamide (60 mL) at 0 °C. Tert-Butyldimethylsilyl chloride (33.3 g) was added to the reaction mass at 1 °C and the resultant reaction mixture was stirred at 27 °C for 15 hours. Water (100 mL) was slowly added to the reaction mass at 17 °C. Ethyl acetate (200 mL) was added to the reaction mass at 17 °C and stirred for 30 minutes. Layers were separated and aqueous layer extracted with ethyl acetate (100 mL). Combined organic layer washed with water (3x100 mL), brine solution (100 mL) and dried with anhydrous sodium sulfate (20 g). The organic layer was concentrated *in vacuo*, the obtained crude product was purified by using column chromatography to afford the titled product.

EXAMPLE 13: Preparation of methyl 2-((2R,4aS,7S,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-methyleneoctahydropyrano[3,2-b]pyran-2-yl)acetate: Methyl 2-((2R,4aS,7S,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-oxooctahydro

pyrano[3,2-b]pyran-2-yl)acetate (13.5 g) and Petasis reagent, $\text{Cp}_2\text{Ti}(\text{CH}_3)_2$ (297 mL) was charged in to round bottom flask under argon atmosphere. Evacuated the reaction mass and released with argon and stirred at 67 °C for 14 hours. Petasis reagent, $\text{Cp}_2\text{Ti}(\text{CH}_3)_2$ (94.5 mL) was added to the reaction mass and stirred at 67 °C 4 hours. Hexane (202.5 mL) was added to the reaction mass at 27 °C and stirred for 30 minutes. Reaction mass was filtered through Celite bed and bed washed with hexane (67.5 mL). Filtrate was concentrated *in vacuo*, the obtained crude product was purified by using column chromatography (eluent: EtOAc/hexane) to afford the titled product.

EXAMPLE 14: Preparation of methyl 2-((2R,4aS,6S,7R,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-(hydroxymethyl)octahydropyrano[3,2-b]pyran-2-yl)acetate: Borane tetrahydrofuran complex solution in THF (65.8 mL) was slowly added to the reaction mass containing methyl 2-((2R,4aS,7S,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-methyleneoctahydropyrano[3,2-b]pyran-2-yl)acetate (16 g) and THF (240 mL) at -5 °C and the resultant reaction mixture was stirred at 28 °C for 3 hours. Water (224 mL) was slowly added to the reaction mass at -30 °C and stirred for 30 minutes. Sodium perborate tetrahydrate (24.27g) was added to the reaction mass at -30 °C and the resultant reaction mass was stirred at 27 °C for 16 hours. Methyl tert-butyl ether (480 mL) and water (160 mL) were added to the reaction mass at 28 °C and stirred for 10 minutes. Layers were separated and aqueous layer was extracted with methyl tert-butyl ether (2x128 mL). Combined organic layer washed with water (2x160 mL) and sodium chloride solution (160 mL). Organic layer was concentrated *in vacuo*, the obtained crude product was purified by using column chromatography (eluent: EtOAc/hexane) to afford the titled product (7.2 g).

EXAMPLE 15: Preparation of methyl 2-((2R,4aS,6R,7R,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-formyloctahydropyrano[3,2-b]pyran-2-yl)acetate: Dess–Martin periodinane (20.7 g) was added to the reaction mass containing methyl 2-((2R,4aS,6S,7R,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-(hydroxymethyl)octahydropyrano[3,2-b]pyran-2-yl)acetate (20.5 g) and dichloromethane (615 mL) at 28 °C under nitrogen atmosphere and the resultant reaction mass was stirred at 28 °C for 4 hours. Sodium thio sulphate solution (205 mL) followed by 10% sodium bicarbonate solution (205 mL) was added to the reaction mass and stirred for 20 minutes. Layers were separated and organic layer was extracted with dichloromethane (2x205 mL). Combined organic layer was washed with 10% sodium bicarbonate solution (102.5 mL), sodium thio sulphate solution (205 mL), water (205

mL) and dried with anhydrous sodium sulfate (30.75 g). Organic layer was concentrated *in vacuo*, the obtained crude product was purified by using column chromatography (eluent: EtOAc/hexane) to afford the titled product (15.7 g).

EXAMPLE 16: Preparation of methyl 2-((2R,4aS,6S,7R,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-((S)-1-hydroxy-3-(trimethylsilyl)prop-2-yn-1-yl)octahydropyrano[3,2-b]pyran-2-yl)acetate: n-Butyl lithium (1.6M hexane, 80.7 mL) was slowly added to the reaction mass containing ethynyltrimethylsilane (19 mL) and toluene (85 mL) at -60 °C under argon atmosphere and the resultant reaction mixture was stirred at -60 °C for 30 minutes. Dimethyl aluminium chloride (1M solution in heptane 141.4 mL) was added to the reaction mass at -60 °C and stirred at -60 °C for 1 hour. Solution containing methyl 2-((2R,4aS,6R,7R,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-formyloctahydropyrano [3,2-b]pyran-2-yl)acetate (8.5 g) in toluene (85 mL) was added to the reaction mass at -60 °C and stirred at -60 °C for 2 hours 15 minutes. Water (85 mL) and ethyl acetate (85 mL) was added to the reaction mass and stirred for 30 minutes. Reaction mass was filtered through Celite bed and bed washed with water (85 mL) and ethyl acetate (85 mL). Filtrate layers were separated and aqueous layer was extracted with ethyl acetate (85 mL). Combined organic layer washed with water (85 mL), 10% sodium chloride solution (170 mL) dried with anhydrous sodium sulfate (4.25 g). Organic layer was concentrated *in vacuo* to afford the titled product.

EXAMPLE 17: Preparation of methyl 2-((2R,4aS,6S,7R,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-((S)-1-hydroxyprop-2-yn-1-yl)octahydropyrano [3,2-b]pyran-2-yl)acetate: Methyl 2-((2R,4aS,6S,7R,8S,8aS)-7,8-bis((tertbutyl dimethylsilyl) oxy)-6-((S)-1-hydroxy-3-(trimethylsilyl)prop-2-yn-1-yl)octahydropyrano [3,2-b]pyran-2-yl)acetate (100 mg), acetone (2 mL), succinimide (33 mg) and silver nitrate (5.65 mg) was charged in to a round bottom flask at 28 °C and the resultant reaction mixture was stirred at 28 °C for 2 hours. The resultant reaction mass was concentrated *in vacuo*, water (5 mL) and ethyl acetate (5 mL) was added to the obtained product and stirred for 5 minutes. Layers were separated and aqueous layer was extracted with ethyl acetate (15 mL). Combined organic layer was washed with water (5 mL) and dried with anhydrous sodium sulfate (200 mg). The resultant reaction mass was concentrated *in vacuo*, the obtained crude product was purified by using column chromatography (eluent: EtOAc/hexane) to afford the titled product (88 mg).

EXAMPLE 18: Preparation of methyl 2-((2R,4aS,6S,7R,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-((S,E)-1-hydroxy-3-(tributylstannyl)allyl)octahydropyrano[3,2-b]pyran-2-yl)acetate: Tetrakis(triphenylphosphine)palladium (826 mg) was added to the reaction mass containing methyl 2-((2R,4aS,6S,7R,8S,8aS)-6-((S)-3-bromo-1-hydroxyprop-2-yn-1-yl)-7,8-bis((tert-butyldimethylsilyl)oxy)octahydropyrano[3,2-b]pyran-2-yl)acetate (8.7 g) at 28 °C under nitrogen atmosphere and then cooled to -72 °C. Tributyltin hydride (7.72 mL) was added to the reaction mass at -72 °C and the resultant reaction mixture was stirred at -70 °C for 2 hours. Reaction mass was transferred in to round bottom flask containing neutral alumina (60.9 g). The resultant reaction mass was concentrated *in vacuo*, the obtained crude product was purified by using column chromatography (eluent: EtOAc/hexane) to afford the titled product (7.6 g).

EXAMPLE 19: Preparation of methyl 2-((2R,4aS,6S,7R,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-((S,E)-1-hydroxy-3-iodoallyl)octahydropyrano[3,2-b]pyran-2-yl)acetate: Iodine (2.95 g) was added to the reaction mass containing methyl 2-((2R,4aS,6S,7R,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-((S,E)-1-hydroxy-3-(tributylstannyl)allyl)octahydropyrano[3,2-b]pyran-2-yl)acetate (8.7 g) and tetrahydrofuran (261 mL) at 0 °C and the resultant reaction mixture was stirred at 0 °C for 1 hour 15 minutes. Ethyl acetate (87 mL) and 5% sodium thiosulfate solution (50 mL) at 0 °C and stirred for 20 minutes. Reaction mass was concentrated *in vacuo*, the obtained product was dissolved in ethyl acetate (87 mL) and water (87 mL) and stirred for 15 minutes. Layers were separated and aqueous layer was extracted with ethyl acetate (87 mL). Combined organic layer washed with water (87 mL) and 10% sodium chloride solution (87 mL). Organic layer was concentrated *in vacuo*, the obtained crude product was purified by using column chromatography (eluent: EtOAc/hexane) to afford the titled product (6.0 g).

EXAMPLE 20: Preparation of methyl 2-((2R,4aS,6S,7R,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-((S,E)-1-((tert-butyldimethylsilyl)oxy)-3-iodoallyl)octahydropyrano[3,2-b]pyran-2-yl)acetate: 2,6-Lutidine (6.3 mL) was added to the reaction mass containing methyl 2-((2R,4aS,6S,7R,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-((S,E)-1-hydroxy-3-iodoallyl)octahydropyrano[3,2-b]pyran-2-yl)acetate (6.0 g) and dichloromethane (180 mL) at -5 °C. Tert-Butyldimethylsilyl trifluoromethanesulfonate (10.44 mL) was added to the reaction mass at -3 °C and the resultant reaction mixture was stirred at 0 °C for 3 hours. Water (90 mL) was added to

the reaction mass at 0 °C and stirred for 10 minutes. Layers were separated and aqueous layer was extracted with dichloromethane (120 mL). Combined organic layer washed with water (90 mL), 10% sodium chloride solution (120 mL) and dried with anhydrous sodium sulfate (6 g). Organic layer was concentrated *in vacuo*, the obtained crude product was purified by using column chromatography (eluent: EtOAc/hexane) to afford the titled product (5.4 g).

EXAMPLE 21: Preparation of methyl 2-((2R,4aS,6R,7R,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-formyloctahydropyrano[3,2-b]pyran-2-yl)acetate:

1,8-Diazabicyclo[5.4.0]undec-7-ene (4.5 g), methyl 2-((2R,4aS,6S,7R,8S,8aS)-7,8-bis((tert-butyldimethylsilyl)oxy)-6-formyloctahydropyrano[3,2-b]pyran-2-yl)acetate (5 g) and dichloromethane (50 mL) was charged in to round bottom flask and the resultant reaction mixture was stirred at 40 °C for 2 hours. 0.2N hydrochloric acid solution (50 mL) was added to the reaction mass at 15 °C and stirred for 10 minutes. Layers were separated, organic layer washed with water (25 mL) and dried with anhydrous sodium sulfate (2.5 g). Organic layer was concentrated *in vacuo*, the obtained crude product was purified by using column chromatography (eluent: EtOAc/hexane) to afford the titled product (2.7 g).

EXAMPLE 22: Preparation of methyl (S,E)-6-(furan-2-yl)-6-hydroxyhex-2-enoate: Nicotinamide adenine dinucleotide (20 mg), Glutamate dehydrogenase –CDX 901 (5 mg), AKR-060 (30 mg) and D-glucose (925 mg) were dissolved in 0.1M potassium phosphate buffer, pH 7 (20 mL). The resultant reaction mixture was added to the methyl (E)-6-(furan-2-yl)-6-oxohex-2-enoate (600 mg) and the reaction mass pH was adjusted to 7 with 10 wt% aqueous potassium carbonate solution. Reaction mass was stirred at 30 °C with 350 rpm for 24 hours at pH 7. Reaction mass pH at 7 was maintained by further additions of 10 wt% aqueous potassium carbonate solution. Reaction mix was extracted with ethyl acetate (2X20 mL) and combined organic layer was dried over magnesium sulphate. Organic layer was concentrated *in vacuo* to afford the titled product as an orange oil.

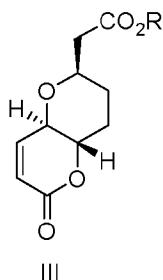
Purity: 99.67%

Yield: 94.8%

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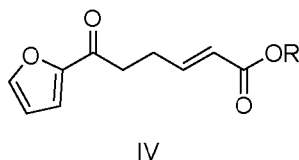
CLAIMS

1. A process for preparation of hexahydropyrano pyran compound of formula III comprising one or more of the following steps:



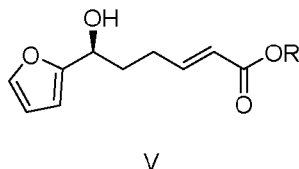
wherein R is C₁-C₈ alkyl group;

(g) converting furan or 2-acetyl furan to a compound of formula IV;



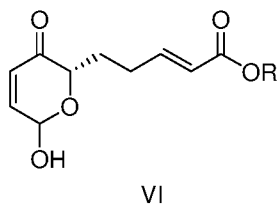
wherein R is C₁-C₈ alkyl group;

(h) reducing compound of formula IV to hydroxy compound of formula V;



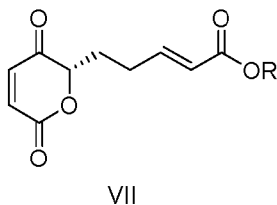
wherein R is C₁-C₈ alkyl group;

(i) converting hydroxy compound of formula V to pyran compound of formula VI;



wherein R is C₁-C₈ alkyl group;

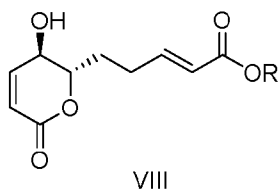
(j) oxidizing compound of formula VI to provide compound of formula VII;



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wherein R is C₁-C₈ alkyl group;

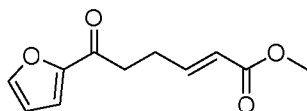
- (k) reducing the compound of formula VII to provide hydroxy compound of formula VIII; and



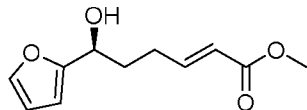
wherein R is C₁-C₈ alkyl group;

- (l) converting hydroxy compound of formula VIII to hexahydropyrano pyran compound of formula III.

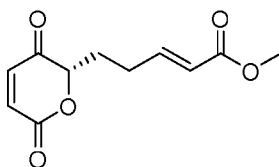
2. The process according to claim 1, wherein compound of formula IV is



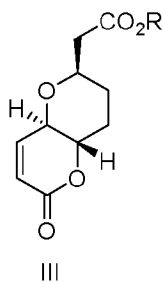
3. The process according to claim 1, wherein compound of formula V is



4. The process according to claim 1, wherein compound of formula VII is



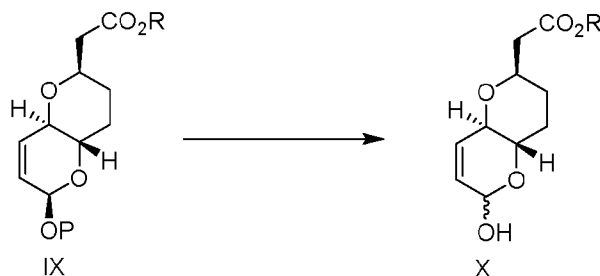
5. A process for preparation of compound of formula III comprising:



-38-

wherein R is C₁-C₈ alkyl group;

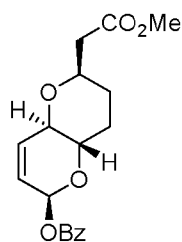
- (c) deprotecting compound of formula IX to provide compound of formula X by using a resin,



wherein R is C₁-C₈ alkyl group, P is an alcohol protected group;

- (d) oxidizing compound of formula X to provide compound of formula III.

6. The process according to claim 5, wherein compound of formula IX is

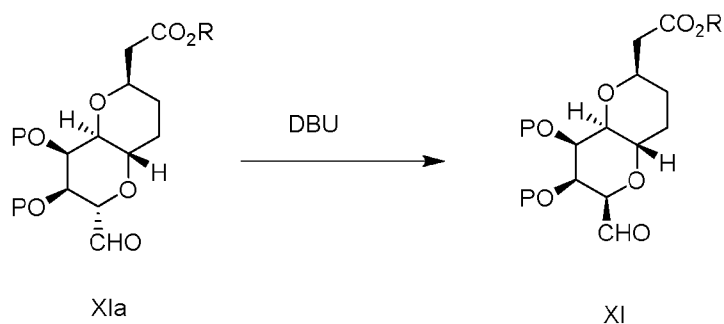


7. The process according to claim 5, wherein the resin is selected from Amberlite IRA-400 chloride form, Amberlite IRA910 chloride form, Ambersep 900 hydroxide form, Amberlite IRA-410 chloride form, Amberlite IRA402 chloride form, Amberlite IRA404 chloride form, Amberlite IRN78 hydroxide form or Amberlyst A26 hydroxide

8. The process according to claim 7, wherein the resin is Amberlite IRA 400 chloride form.

9. A process for isomerization of a compound of formula XIa to a compound of formula XI using 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) in halogenated hydrocarbon solvent.

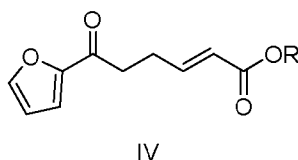
-39-



wherein P is an alcohol protected group and R is C₁-C₈ alkyl group

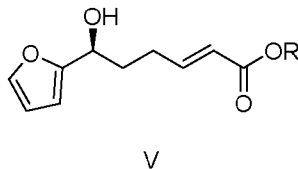
10. A process of claim 9 wherein a compound of formula XIa is prepared from a compound of formula III obtained according to a process of claim 1 or claim 5.

11. A compound of formula IV.



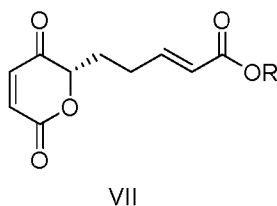
wherein R is C₁-C₈ alkyl group;

12. A compound of formula V or isomers thereof.



wherein R is C₁-C₈ alkyl group;

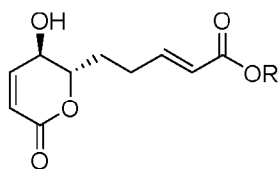
13. A compound of formula VII or isomers thereof.



wherein R is C₁-C₈ alkyl group;

14. A compound of formula VIII or isomers thereof.

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VIII

wherein R is C₁-C₈ alkyl group;

15. A process for preparation of eribulin or a pharmaceutically acceptable salt thereof from a compound of any one of claims 1-14.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2017/051749

A. CLASSIFICATION OF SUBJECT MATTER
C07D491/22, C07D493/22 Version=2017.01

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)

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	IN-CHE-2013-03529 (A) DR REDDY'S LABORATORIES LIMITED IN Pub Date 13-Feb-2015. See: formula IX, formula XI -----	12, 14 & 11, 13
Y	IN-CHE-2013-03529 (A) DR REDDY'S LABORATORIES LIMITED IN Pub Date 13-Feb-2015. WHOLE DOCUMENT -----	1-10 & 15
Y	US5436238 (A) HARVARD COLLEGE (US) Pub. Date 25-Jul-1995 See: Column 27; Column 50; -----	1-8
Y	FI72119 (B) PFIZER[US] Publication Date 31-Dec-1986. See: PAGE 4 FORMULA III to formula I. -----	1-4
Y	IN-MUM-2013-00508A LUPIN LIMITED (IN) Pub. Date 28-Nov-2014. See: Isomerization, Claim 6 (DBU) -----	9-10
Y	DE60112024 (T2) FARMABIOS SPA (IT) Pub. Date 20-Apr-2006 See: Isomerization, Claims1-9 (DBU)	9-10



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

26-08-2017

Date of mailing of the international search report

26-08-2017

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2017/051749

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	----- WO2016003975 (A1) HARVARD COLLEGE [US] Publication Date 07.01.2016 See: schemes 2-8, claims 35-49 -----	15
Y	----- J. Am. Chem. Soc., 2015, 137 (19), pp 6219-6225 DOI: 10.1021/jacs.5b03498 See: schemes 1 & 2 -----	15
Y	----- J. Am. Chem. Soc., 2015, 137 (19), pp 6226-6231 DOI: 10.1021/jacs.5b03499 See: Schemes 2, 7, & 8 -----	15

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2017/051749

Citation	Pub.Date	Family	Pub.Date
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		EP 0642345 A1	15-03-1995
		JP H07504664 A	25-05-1995
		WO 9317690 A1	16-09-1993
FI 72119 B	31-12-1986	AU 2601777 A	21-09-1978
		CA 1095921 A	17-02-1981
		JP S5318578 A	20-02-1978
		US 4082717 A	04-04-1978
WO 2016003975 A1	07-01-2016	EP 3160970 A1	03-05-2017
		JP 2017520586 A	27-07-2017
		US 2017137437 A1	18-05-2017