

MALTOL ETHER PROCESSES AND INTERMEDIATES

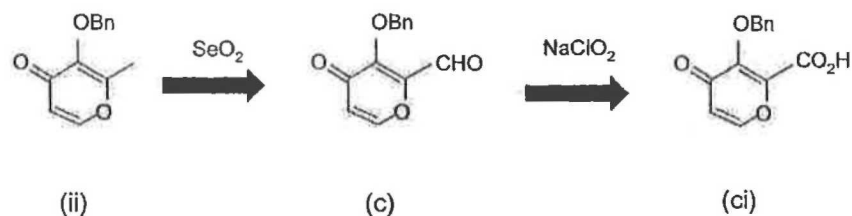
FIELD OF THE INVENTION

5 The present invention generally relates to synthetic organic reaction sequences that provide a key intermediate in the production of medicinal compounds useful as HIV integrase inhibitors in the treatment of viral diseases, in particular, the treatment of HIV infection.

BACKGROUND OF THE INVENTION

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WO 2006/116764 published November 2, 2006 to Shionogi & Co. Ltd of Osaka, Japan teaches various polycyclic carbamoylpyridone compounds having HIV integrase activity. At page 113, there is described a reaction sequence as follows:

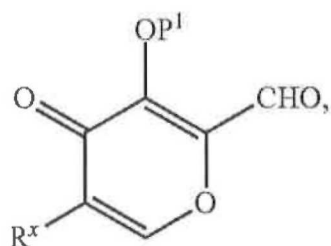


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whereby selenium dioxide is added to a solution of the benzyl ether of maltol designated above as (ii), heating the mixture to 160° C , recovering aldehyde (c) and then oxidizing the aldehyde with sodium chlorate to yield carboxylic acid (ci).

SUMMARY

In one aspect, there is provided a process of producing an aldehyde of formula 1,

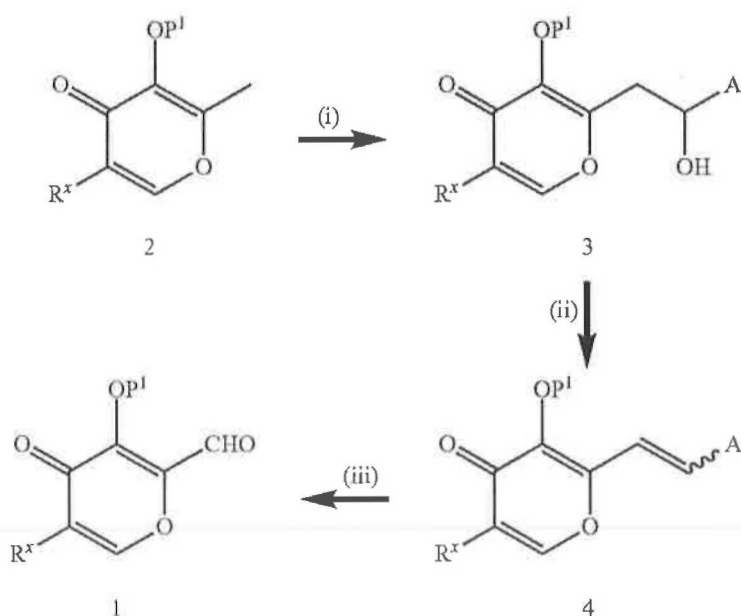


which comprises the steps of:

(i) reacting a pyrone of formula 2 with an aldehyde of formula A-CHO to produce an alcohol of formula 3;

(ii) reacting the alcohol of the formula 3 with a dehydrating reagent to produce a triene of formula 4; and

(iii) reacting the triene of the formula 4 with an oxidating reagent to produce the aldehyde of the formula 1,



wherein:

P^I is hydrogen or a hydroxyl protecting group;

R^x is halogen or $R^2-X-NR^1-C(O)-$;

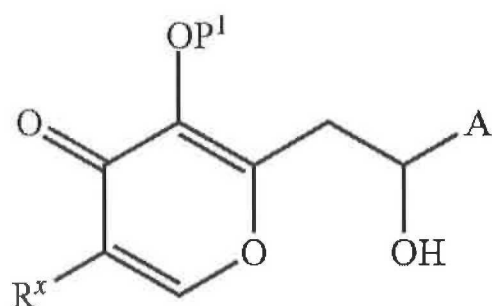
R^1 is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from the group consisting of O, S, SO, SO₂ and NH, a loweralkylene or a loweralkylene wherein each alkyl may be intervened by a heteroatom;

R² is optionally substituted aryl; and

A is aryl.

In another aspect, there is provided an alcohol of the following formula 3:



wherein:

P¹ is hydrogen or a hydroxyl protecting group;

R^x is halogen or R²-X-NR¹-C(O)-;

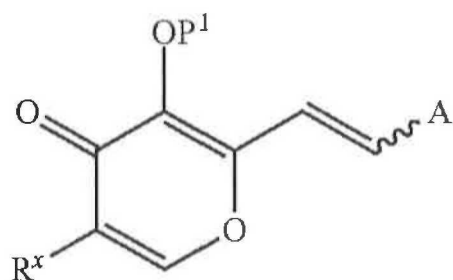
R¹ is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from the group consisting of O, S, SO, SO₂ and NH, a loweralkylene or a loweralkylene wherein each alkyl may be intervened by a heteroatom;

R² is optionally substituted aryl; and

A is aryl.

In another aspect, there is provided a triene of the following formula 4:



wherein:

P¹ is hydrogen or a hydroxyl protecting group;

R^x is halogen or R²—X—NR¹—C(O)—;

R¹ is hydrogen or lower alkyl;

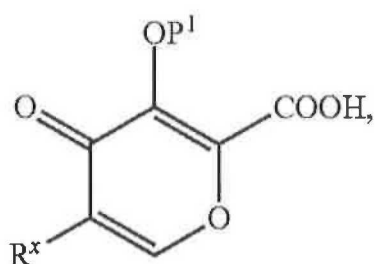
X is a single bond, a heteroatom group selected from the group consisting of O, S, SO, SO₂ and NH, a loweralkylene or lowerlalkylene a loweralkylene wherein each alkyl may be intervened by a heteroatom;

R² is optionally substituted aryl;

A is aryl; and

the wavy line bond is either cis or trans.

In another aspect, there is provided a process of producing a carboxylic acid of formula 5,



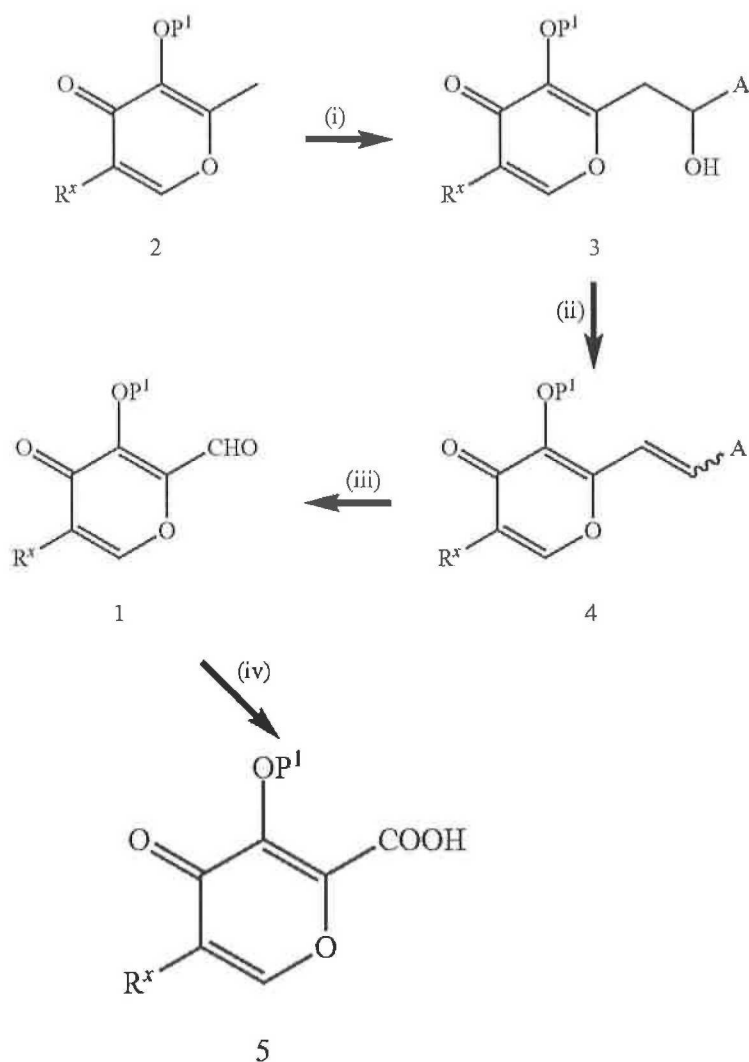
which comprises the steps of:

(i) reacting a pyrone of formula 2 with an aldehyde of formula A-CHO to produce an alcohol of formula 3;

(ii) reacting the alcohol of the formula 3 with a dehydrating reagent to produce a triene of formula 4;

(iii) reacting the triene of the formula 4 with an oxidating reagent to produce an aldehyde of formula 1: and

(iv) oxidizing the aldehyde of the formula 1 to produce the carboxylic acid of the formula 5,



wherein:

P^1 is hydrogen or a hydroxyl protecting group;

R^x is halogen or $R^2-X-NR^1-C(O)-$;

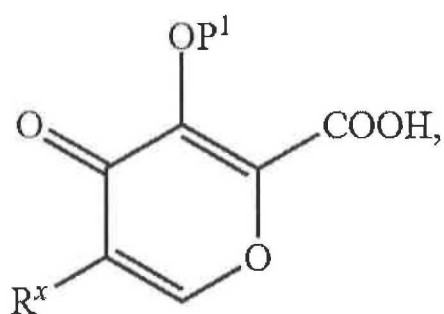
R^1 is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from the group consisting of O, S, SO, SO_2 --and NH, a loweralkylene or loweralkylene a loweralkylene wherein each alkyl may be intervened by a heteroatom;

R^2 is optionally substituted aryl; and

A is aryl.

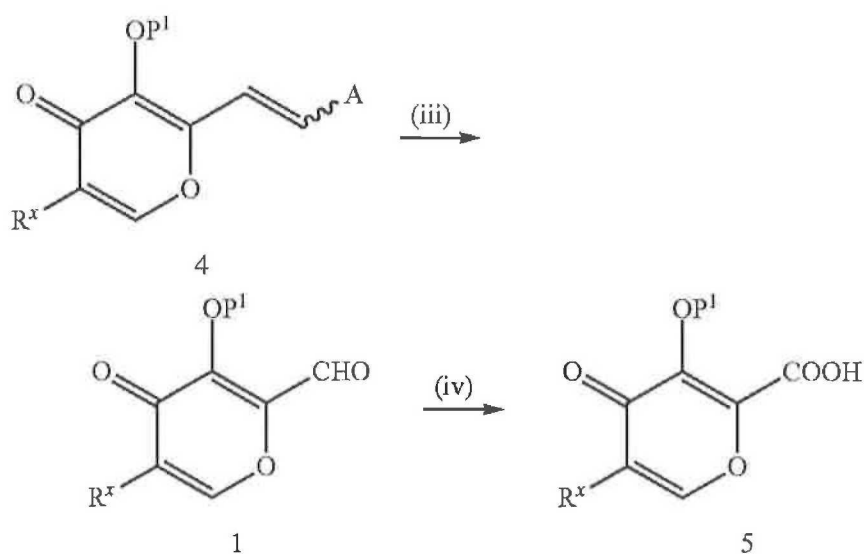
In another aspect, there is provided a process of producing a carboxylic acid of formula 5,



which comprises the steps of:

(iii) reacting a triene of formula 4 with an oxidating reagent to produce an aldehyde of formula 1; and

(iv) oxidizing the aldehyde of the formula 1 to produce the carboxylic acid of the formula 5,



wherein:

P¹ is hydrogen or a hydroxyl protecting group;

Rˣ is halogen or R²—X—NR¹—C(O)—;

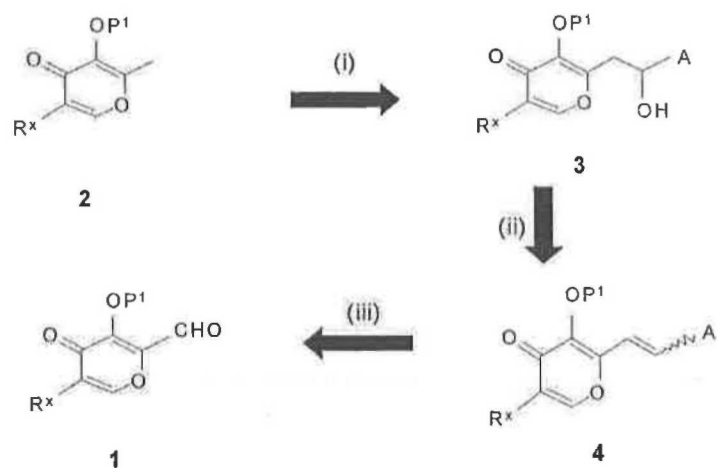
R¹ is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from the group consisting of O, S, SO, SO₂ and NH, a loweralkylene or a loweralkylene wherein each alkyl may be intervened by a heteroatom;

R² is optionally substituted aryl; and

A is aryl.

In one embodiment, there is provided a process for preparing an aldehyde of the following formula 1 from the corresponding methyl compound of formula 2 without the use of a highly toxic selenium reagent:

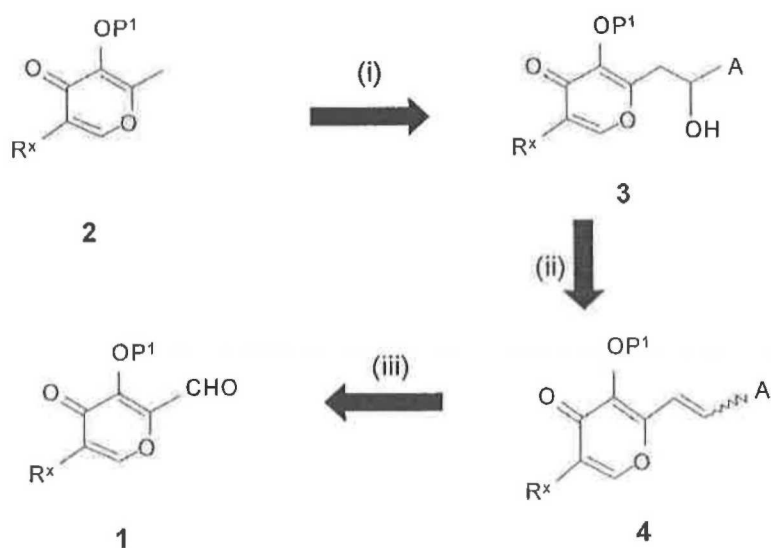


The process comprises the steps of:

- i) aldol reaction of **2** with an aldehyde of formula $A-CHO$ to produce the alcohol **3**;
- ii) elimination reaction of the alcohol **3** to produce the triene **4**; and
- iii) oxidative cleavage of the triene **4** to produce the aldehyde of formula **1**.

DETAILED DESCRIPTION OF THE INVENTION

The present invention features a process of producing an aldehyde of the formula **1**;



wherein

P^1 is hydrogen or a hydroxyl protecting group;

R^x is hydrogen, halo, or $R^2-X-NR^1-C(O)-$;

R¹ is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO₂, and NH or loweralkylene or lowerlalkylene wherein each may be intervened by a heteroatom;

R² is optionally substituted aryl; and

5 A is alkyl or aryl,

which comprises the steps of:

i) reacting pyrone **2** with an aldehyde of formula A-CHO to produce the alcohol **3**;

ii) reacting the alcohol **3** with a dehydrating reagent to produce the triene **4**; and

10 iii) reacting the triene **4** with an oxidating reagent to produce the aldehyde of formula **1**.

The present invention also features a process as described above, wherein P¹ and R^x are hydrogen, A is phenyl and the wavy line bond in triene **4** is a trans bond. Another preferable
15 aspect is that P¹ is hydroxyl protecting group, R^x is hydrogen, A is phenyl and the wavy line bond in triene **4** is a trans bond.

The present invention also features a process as described above, wherein step (i) is conducted in the presence of a base.

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The present invention also features a process as described above, wherein step (ii) is conducted in the presence of base.

The present invention also features a process as described above, wherein the oxidating reagent is preferably ruthenium reagent. The ruthenium reagent is preferably ruthenium
25 tetroxide generated in situ.

The term "lower alkyl", alone or in combination with any other term, refers to a straight-chain or branched-chain saturated aliphatic hydrocarbon radical containing 1 to 6 carbon atoms. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-
30 butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl and the like. The term "lower alkyl" is preferably C1-C4 alkyl.

The term "lower alkylene" refers to a straight or branched chain divalent hydrocarbon radical, preferably having from one to six carbon atoms, unless otherwise defined. Examples of
35

"alkylene" as used herein include, but are not limited to, methylene, ethylene, propylene, butylene, isobutylene and the like. The term "lower alkylene" is preferably C1-C4 alkylene.

5 The term "lower alkenylene" refers to a straight or branched chain divalent hydrocarbon radical, one or two carbon-carbon double bonds. The term "lower alkenylene" is preferably C2-C4 alkylene

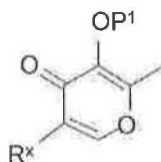
The term "halo" or "halogen" refers fluorine (F), chlorine (Cl), bromine (Br), or iodine (I).

10 The term "aryl" alone or in combination with any other term, refers to a carbocyclic aromatic moiety (such as phenyl or naphthyl) containing 6 carbon atoms, and more preferably from 6-10 carbon atoms. Examples of aryl radicals include, but are not limited to, phenyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl, indanyl, phenanthridinyl and the like. Unless otherwise indicated, the term "aryl" also includes each
15 possible positional isomer of an aromatic hydrocarbon radical, such as in 1-naphthyl, 2-naphthyl, 5-tetrahydronaphthyl, 6-tetrahydronaphthyl, 1-phenanthridinyl, 2-phenanthridinyl, 3-phenanthridinyl, 4-phenanthridinyl, 7-phenanthridinyl, 8-phenanthridinyl, 9-phenanthridinyl and 10-phenanthridinyl. Examples of aryl radicals include, but are not limited to, phenyl, naphthyl, indenyl, azulenyl, fluorenyl, anthracenyl, phenanthrenyl, tetrahydronaphthyl,
20 indanyl, phenanthridinyl and the like. The term "aralkyl" refers to an alkyl group substituted by an aryl. Examples of aralkyl groups include, but are not limited to, benzyl and phenethyl. The term "aryl" is preferably phenyl.

Optional substituents on aryl are one or two group selected from hydroxy, halogen, amino and
25 lower alkyl.

"Hydroxyl Protecting group" may be selected from groups known to those skilled in the art, including protecting groups disclosed in Greene, Theodora W.; Wuts, Peter G. M.. Protective Groups in Organic Synthesis. 2nd Ed. (1991), 473 pp. or Kocienski, Philip J. Protecting
30 Groups. 3rd Ed. 2005, (2005), 679 pp. Preferred is alkyl or arylalkyl (e.g., benzyl).

The starting material of the invention process may be a pyrone of the following formula 2:



2

wherein

P¹ is hydrogen or a hydroxyl protecting group;

R^x is hydrogen, halo such as Br, or R²-X-NR¹-C(O)-;

5 R¹ is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO₂, and NH or loweralkylene or lowerlalkylene wherein each may be intervened by a heteroatom; and

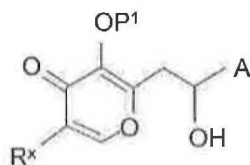
R² is optionally substituted aryl.

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In one of preferable embodiments, P¹ is hydroxyl protecting group such as arylalkyl (e.g., benzyl (: Bn)), R^x is hydrogen.

For the aldehyde A-CHO used in step (i) to produce the alcohol 3, A may be an alkyl or aryl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl, phenyl or substituted phenyl and preferred is phenyl:

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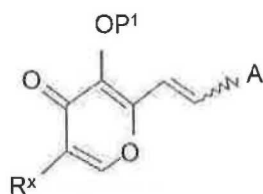
The step (i) is conducted preferably in the presence of a base such as LiHMDS, NaHMDS, 20 KHMDS, LDA, KDA, NaOEt or KOtBu and preferred is LiHMDS.

The reaction is conducted at about -100°C to under ice-cooling and preferably at -80°C to -50°C.

The reaction solvent is such as THF, DME, diglyme, TBME, or CPME and preferably THF.

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The product of the elimination step (ii) is the triene **4** wherein the wavy bond depicted is indicative of either a cis or trans configuration, preferably trans being the expected product:



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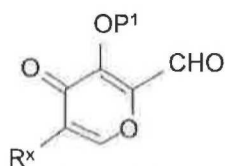
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The step (ii) is conducted preferably in the presence of a base such as Et₃N, iPr₂NEt, or DBU. More preferably, compound **3** may be activated in advance by an activating reagent such as mesylating (e.g., MsCl), tosylating reagent (e.g., TsCl) or chlorinating (e.g., SOCl₂).

- 10 The reaction temperature is preferably 0°C to 100°C, preferably 0°C to 40 °C, more preferably around room temperature.

The reaction solvent is preferably THF, DME, DMF, DMA, NMP or MeCN, and more preferably THF.

- 15 The catalytic system used in step (iii) to produce the aldehyde **1** may be oxidizing reagent, preferably ruthenium reagent. The ruthenium reagent is preferably ruthenium tetroxide, which may be generated in situ from RuCl₃/NaIO₄ or RuCl₃/HIO₄.

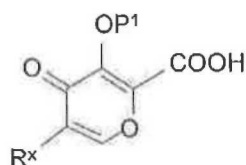


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In the above formulas **3**, **4** and **1**, the moieties P¹ and R^x are as defined for pyrone **2** and A in triene **4** is as defined for alcohol **3**.

- 25 A further aspect of the invention is the step of oxidizing the aldehyde of formula **1** to yield the carboxylic acid of formula **5** in a step (iv):



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wherein P¹ and R^x are as defined above for the pyrone of formula 2.

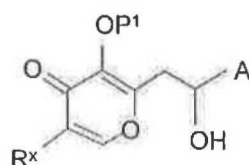
In step (iv), the oxidizing reagent used in step (iv) is preferably sodium chlorite or sodium hypochlorite.

The reaction temperature is preferably 0°C to 100°C, preferably 0°C to 40 °C, more preferably 5°C to 20 °C.

The reaction solvent is preferably DMF, MeCN, AcOEt, water or a mixture thereof etc.

Also part of the present invention are novel intermediates such as those novel compounds of formulae 3 and 4.

The present invention also features an alcohol of the following formula 3:



3

wherein

P¹ is hydrogen or a hydroxyl protecting group;

R^x is hydrogen, halo, or R²-X-NR¹-C(O)-;

R¹ is hydrogen or lower alkyl;

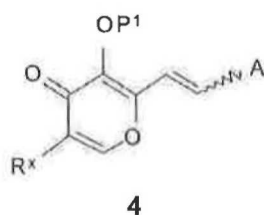
X is a single bond, a heteroatom group selected from O, S, SO, SO₂, and NH or loweralkylene or lowerlalkylene wherein each may be intervened by a heteroatom;

R² is optionally substituted aryl; and

A may be an alkyl or aryl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl, phenyl or substituted phenyl and preferred is phenyl:

An alcohol as described above, wherein P¹ and R^x are hydrogen, and A is phenyl is included within the invention.

The present invention features a triene of the following formula 4:



wherein

P¹ is hydrogen or a hydroxyl protecting group;

5 R^x is hydrogen, halo, or R²-X-NR¹-C(O)-;

R¹ is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from O, S, SO, SO₂, and NH or loweralkylene or loweralkylene wherein each may be intervened by a heteroatom;

R² is optionally substituted aryl; and

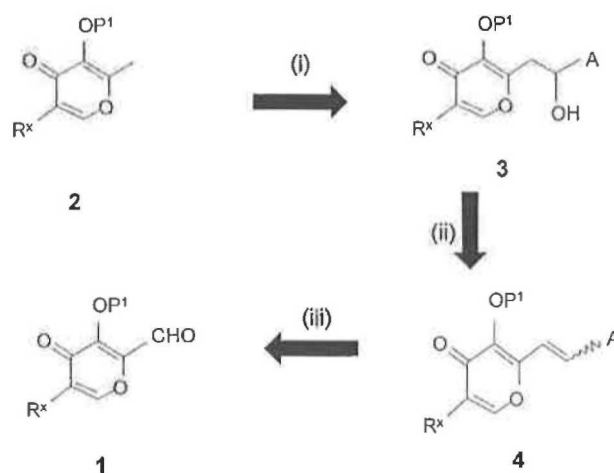
10 A may be an alkyl or aryl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl, phenyl or substituted phenyl and preferred is phenyl; and

the wavy line bond is either cis or trans.

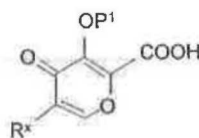
15 In the triene as described above, P¹ and R^x may be hydrogen, A may be phenyl and the wavy line bond may be trans.

The present invention features a process for producing a carboxylic acid of the following formula 5:

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(iv)



5

wherein

- 5 P¹ is hydrogen or a hydroxyl protecting group;
R^x is hydrogen, halo, or R²-X-NR¹-C(O)-;
R¹ is hydrogen or lower alkyl;
X is a single bond, a heteroatom group selected from O, S, SO, SO₂, and NH or loweralkylene or lowerlalkylene wherein each may be intervened by a heteroatom;
10 R² is optionally substituted aryl; and
A may be an alkyl or aryl group such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl, phenyl or substituted phenyl and preferred is phenyl;

which comprises the steps of:

- 15 i) reacting pyrone 2 with an aldehyde of formula A-CHO to produce the alcohol 3;
ii) reacting the alcohol 3 with a dehydrating reagent to produce the triene 4;
iii) reacting the triene 4 with a ruthenium reagent to produce the aldehyde of formula 1; and
1: and
IV) oxidizing the aldehyde of formul 1 to produce the carboxylic acid of formula 5.

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EXAMPLES

In this specification, each abbreviations represent as follows.

THF : tetrahydrofuran

25 DME : dimethoxyethan

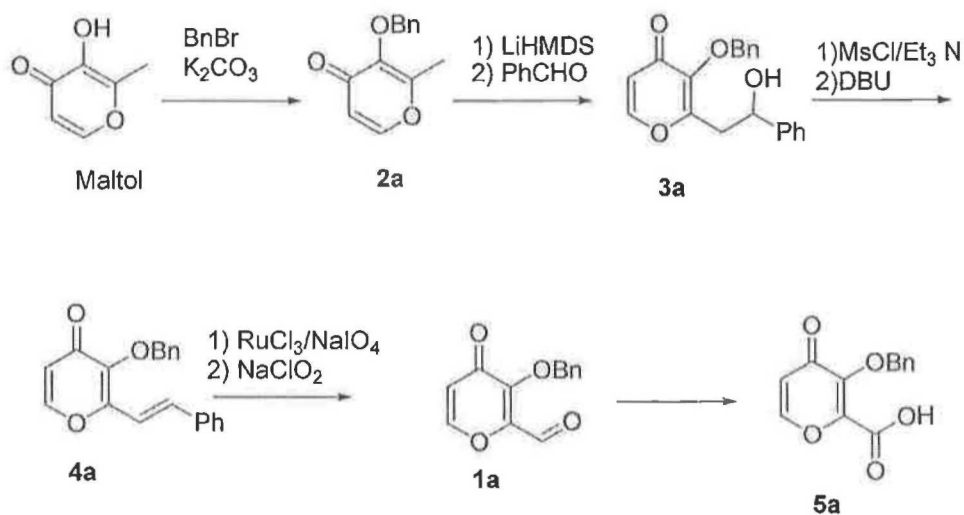
diglyme : ethyleneglycol dimethyl ether

DMF : *N,N*-dimethylformamide

DMA : *N,N*-dimethylacetamide

- TBME : *t*-butyl methyl ether
 CPME : cyclopentyl methyl ether
 LiHMDS : lithium hexamethyldisilazane
 NaHMDS : sodium hexamethyldisilazane
 5 KHMDS : potassium hexamethyldisilazane
 LDA : lithium diisopropylamide
 KDA : potassium diisopropylamide
 NaOEt : sodium ethoxide
 NaOtBu : sodium *tert*-butoxide
 10 KOtBu : potassium *tert*-butoxide
 Me : methyl
 Bn : benzyl
 Ph : phenyl
 Et₃N : triethylamine
 15 MsCl : methanesulfonyl chloride
 TsCl : toluenesulfonyl chloride
 DBU : 1,8-diazabicyclo [5.4.0] undec-7-ene
 TEMPO : 2,2,6,6-tetramethylpiperidine 1-oxyl
 NMP : N-methylpyrrolidone
 20 AcOEt : ethyl acetate

The reaction steps are shown below,



Reference Example A

Page 113 of WO 2006/116764 going from 2 to 100 to 101 with the narratives 1) and 2) of
5 page 113.

Example A

Maltol to Benzylmaltol 2a

Maltol: 2000g

BnBr: [MW=171.04, d=1.444] 2848.2g (1.05eq)

10 K₂CO₃ [MW=138.21] 2630.3g (1.2eq)

MeCN 14L 7V

To the solution of 2000g of **Maltol** in MeCN (14L) was added BnBr (2848.2g) and K₂CO₃
(2630.3g) at room temperature. (around 23°C)

15 After addition of reagent, the temperature of the reaction mixture was getting high.

This reaction mixture was kept at 80°C for 5hr and then cooled down to room temperature.

The reaction mixture was filtered and washed with MeCN (3L, 1L, 1L). Filtration was
concentrated and added THF 2L and concentrated again. (check the KF 1.33%).

THF 1.5L was added to the residue and concentrate again. (KF= 0.135%)

20 The residue **2a** : 3648g

Example 1.1

Benzylmaltol 2a to 3-Benzylloxy-2-(2-hydroxy-2-phenyl-ethyl)-pyran-4-one 3a

25 **2a** :2300g

1.0M LiHMDS in THF :12.5L (1.25eq)

PhCHO [MW= 106.12]: 1273.4g (1.2eq)

To the solution of **2a** (2300g) in THF 14.9L was cooled down to -60°C and added LiHMDS
30 12.5L and PhCHO (1273.4g) in THF 2.0L. (temp:-60°C). The reaction mixture was stirred
for 1hr at -60°C

This reaction mixture was poured into ice water 19.5L(9V) and conc. HCl 2.9L (1.34V) and
AcOEt 10.8L (5V). The organic layer was washed with H₂O 6.3L twice and concentrated
and toluene was added 4L and concentrated again. To this residue was added toluene 4L

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and cooled down to 0°C. The suspension was filterated and washed with toluene 2L. 2326g of **3a** was obtained (72% from **Maltol**).

Example 1.2

5 **3-Benzylloxy-2-(2-hydroxy-2-phenyl-ethyl)-pyran-4-one 3a to 3-Benzylloxy-2-((E)-styryl)-pyran-4-one 4a**

3a [MW=322.35] 882.3g

THF 8.8L (10V)

TEA [MW=101.19] 415.5g (1.5eq)

10 MsCl [MW=114.54] 407.5g (1.3eq)

NMP 440mL

DBU [MW=152.24] 1166.8g (2.8eq)

To the solution of **3a** and TEA in THF (8.8L) was added dropwise MsCl at room
15 temperature. (22.8°C-29°C) and stirred for 30min. (TLC check). After addition of NMP to
this reaction mixture, DBU was added dropwise over 1hr. (25-27°C), followed by dropwise
addition of 1.76L solution: 1:4 mixture of 62% H₂SO₄:13%NaCl. (16-27°C) The reaction
mixture was extracted with AcOEt, and the extracts was washed with 2%Na₂SO₃aq. The
organic layer was evaporated in vaccuo and 5V of toluene was added, again evaporated.
20 Evaporation was stopped when volume was reduced to ca 2V. After crystalline appears
(seeding is preferred), 6V of hexane was added and cooled with an ice bath. Crystalline
solid was collected by filtration and washed with 2V of hexane. A second lot was conducted
and 1559.6g of compound **4a** was obtained (93.6% yield).

25 Example 1.3

3-Benzylloxy-2-((E)-styryl)-pyran-4-one 4a to 3-Benzylloxy-4-oxo-4H-pyran-2-carbaldehyde 1a

4a [MW=304.34] 870.7g

30 RuCl₃.nH₂O [MW=207.43] 13.06g(2.2mol%)

NaIO₄ [MW=213.88] 2.45kg (4eq)

CH₃CN 2.6L(3V)

AcOEt 2.6L(3V)

H₂O 2.6L(3V)

35

To a mixture of 10.0 g of compound **4a** and 13.6 mg of $\text{RuCl}_3 \cdot n\text{H}_2\text{O}$ in 95 mL of MeCN and 10 mL of water, mixture of 155mL of water, 7.2 g of hydrosulfuric acid, and 15.5 g of NaIO_4 was added for 2.5 h at 20 °C. After aging for 1 h, organic and aqueous layers were separated and aqueous layer was extracted by 30mL of AcOEt. Aqueous layer was extracted again by 5 30mL of ethyl acetate and organic layers were combined. 6 mL of 5% NaHSO_3 solution was added to the combined organic layer and the layers were separated. The organic layer was adjusted to pH 6.0 by adding 4.0g of 2M NaOH solution and the aqueous layer was separated. After 60 mL of 5% NaHCO_3 solution and 257mg of TEMPO was added, 25.9 g of NaClO solution was added to the reaction mixture at 25 °C for 1h and stirred for 30min to 10 check the reaction was finished. After the layers were separated, 42.5mL of 5% Na_2SO_3 solution and 30mL of AcOEt were added and separated. The aqueous layer was extracted by 30mL of AcOEt and separated. 12% H_2SO_4 was added to the reaction mixture at 20 °C for 1h and the mixture was cooled to 5 °C. After the mixture was stirred for 30 min, the mixture was filtered, washed with 30 mL of water twice and dried to provide 5.7 g of compound **5a** (70% 15 yield) as a crystal.

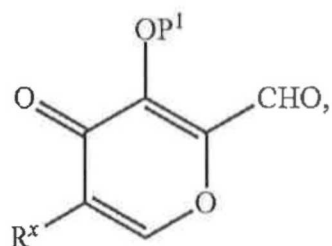
compound **5a** :

^1H NMR(300 MHz, CDCl_3) δ 7.78 (d, J = 5.7 Hz, 1H), 7.54–7.46 (m, 2H), 7.40–7.26 (m, 3H), 6.48 (d, J = 5.7 Hz, 1H), 5.6 (brs, 1H), 5.31 (s, 2H).

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What is claimed is:

1. A process of producing an aldehyde of formula 1,

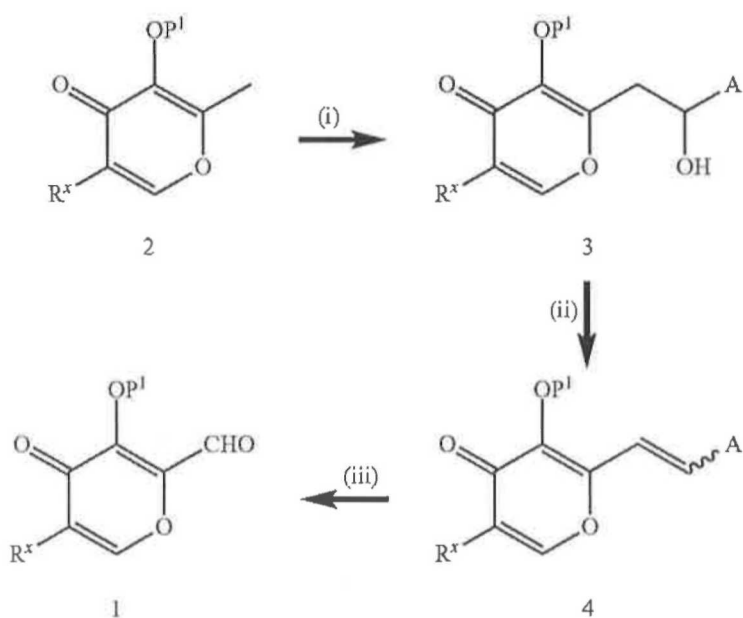


which comprises the steps of:

(i) reacting a pyrone of formula 2 with an aldehyde of formula A-CHO to produce an alcohol of formula 3;

(ii) reacting the alcohol of the formula 3 with a dehydrating reagent to produce a triene of formula 4; and

(iii) reacting the triene of the formula 4 with an oxidating reagent to produce the aldehyde of the formula 1,



wherein:

P¹ is hydrogen or a hydroxyl protecting group;

R^x is halogen or R²-X-NR¹-C(O)-;

R¹ is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from the group consisting of O, S, SO, SO₂ and NH, a loweralkylene or a loweralkylene wherein each alkyl may be intervened by a heteroatom;

R² is optionally substituted aryl; and

A is aryl.

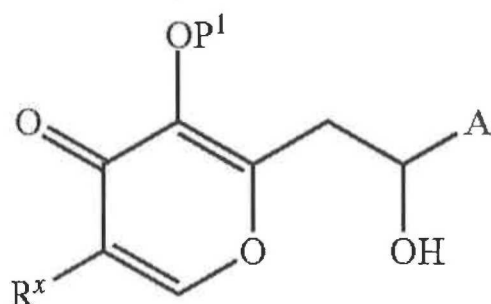
2. The process of claim 1, wherein step (i) is reacted in the presence of a base.

3. The process of claim 1, wherein step (ii) is reacted in the presence of a base.

4. The process of claim 1, wherein the oxidating reagent is a ruthenium reagent.

5. The process of claim 1, wherein the ruthenium reagent is ruthenium tetroxide generated in situ.

6. An alcohol of the following formula 3:



wherein:

P¹ is hydrogen or a hydroxyl protecting group;

R^x is halogen or R²—X—NR¹—C(O)—;

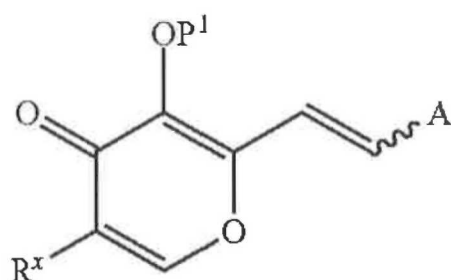
R¹ is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from the group consisting of O, S, SO, SO₂ and NH, a loweralkylene or a loweralkylene wherein each alkyl may be intervened by a heteroatom;

R² is optionally substituted aryl; and

A is aryl.

7. A triene of the following formula 4:



wherein:

10 P^1 is hydrogen or a hydroxyl protecting group;

R^x is halogen or $R^2-X-NR^1-C(O)-$;

R^1 is hydrogen or lower alkyl;

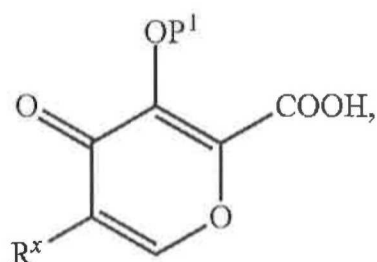
X is a single bond, a heteroatom group selected from the group consisting of O, S, SO, SO_2 and NH, a loweralkylene or loweralkylene a loweralkylene wherein each alkyl may
15 be intervened by a heteroatom;

R^2 is optionally substituted aryl;

A is aryl; and

the wavy line bond is either cis or trans.

20 8. A process of producing a carboxylic acid of formula 5,



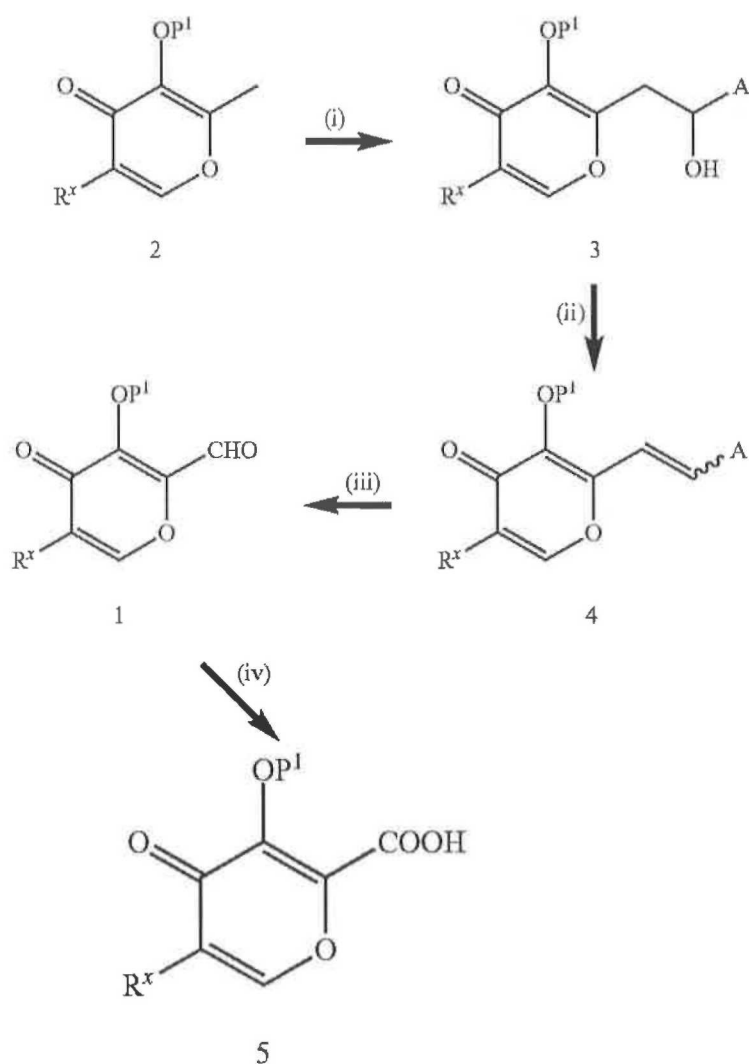
which comprises the steps of:

30 (i) reacting a pyrone of formula 2 with an aldehyde of formula $A-CHO$ to produce an alcohol of formula 3;

(ii) reacting the alcohol of the formula 3 with a dehydrating reagent to produce a triene of formula 4;

(iii) reacting the triene of the formula 4 with an oxidating reagent to produce an
35 aldehyde of formula 1: and

(iv) oxidizing the aldehyde of the formula 1 to produce the carboxylic acid of the formula 5,



wherein:

P^1 is hydrogen or a hydroxyl protecting group;

R^x is halogen or $R^2-X-NR^1-C(O)-$;

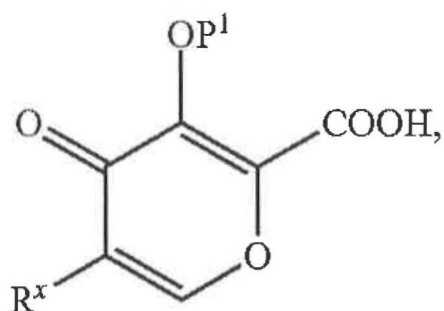
R^1 is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from the group consisting of O, S, SO, SO_2 --and NH, a loweralkylene or lowerlalkylene a loweralkylene wherein each alkyl may be intervened by a heteroatom;

R^2 is optionally substituted aryl; and

A is aryl.

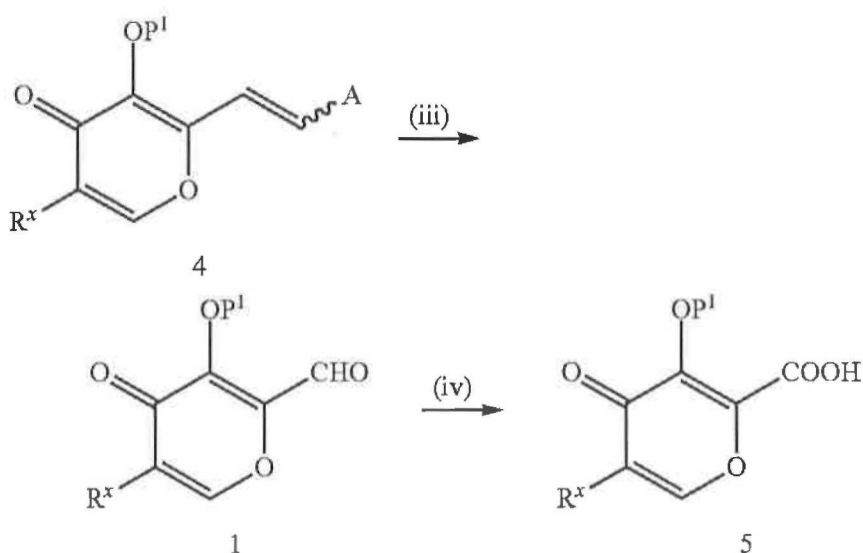
9. A process of producing a carboxylic acid of formula 5,



which comprises the steps of:

10 (iii) reacting a triene of formula 4 with an oxidating reagent to produce an aldehyde of formula 1; and

(iv) oxidizing the aldehyde of the formula 1 to produce the carboxylic acid of the formula 5,



wherein:

P¹ is hydrogen or a hydroxyl protecting group;

Rˣ is halogen or R²—X—NR¹—C(O)—;

30 R¹ is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from the group consisting of O, S, SO, SO₂ and NH, a loweralkylene or a loweralkylene wherein each alkyl may be intervened by a heteroatom;

R² is optionally substituted aryl; and

35 A is aryl.