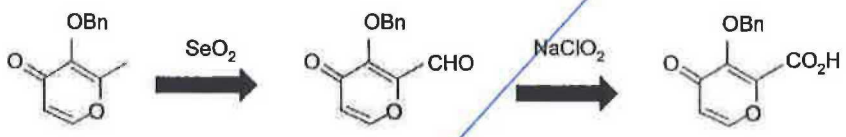
# MALTOL ETHER PROCESSES AND INTERMEDIATES

## FIELD OF THE INVENTION

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

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:




(ii) (c) (ci)

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 OF THE INVENTION

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:

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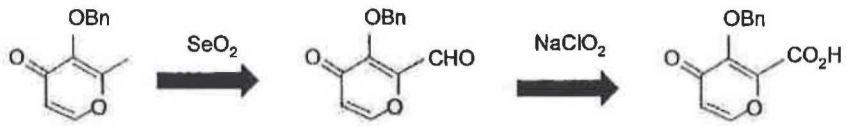


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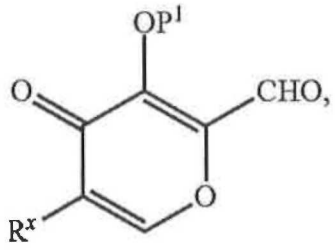
whereby selenium dioxide is added to a solution of the benzyl ether of maltol designated above as (ii), heating the mixture to 160° C , recovering aldehyde (c) and then oxidizing the aldehyde with sodium chlorate to yield carboxylic acid (ci).

## SUMMARY

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

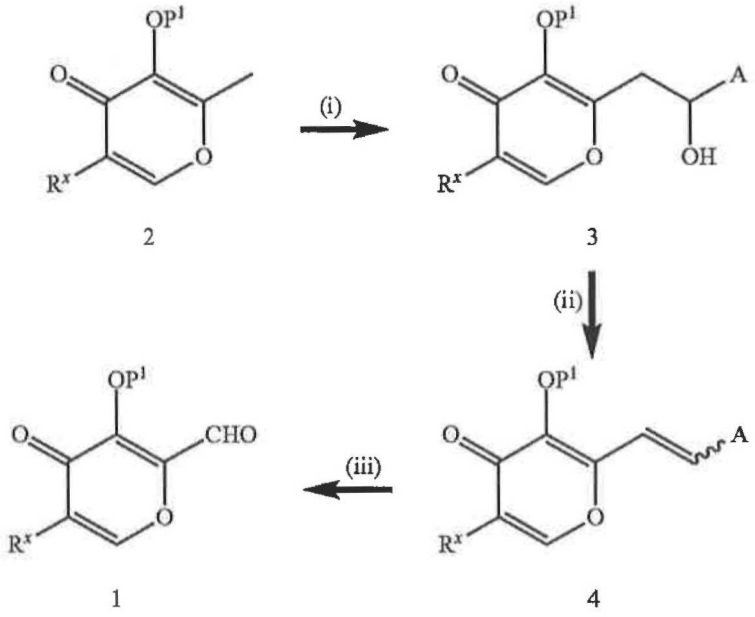


which comprises the steps of:

(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:

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

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

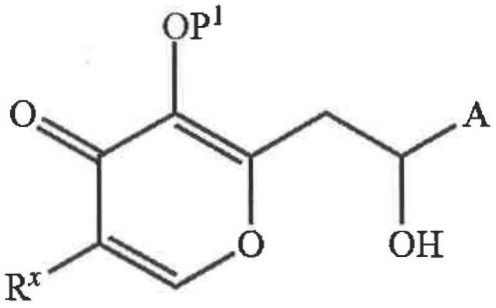
$R^1$ is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from the group consisting of O, S, SO, $SO_2$ and NH, a loweralkylene or 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 an alcohol of the following formula 3:




wherein:

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

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

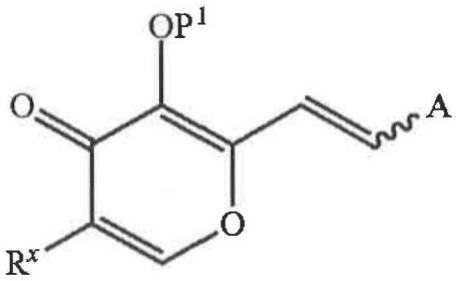
$R^1$ is hydrogen or lower alkyl;

X is a single bond, a heteroatom group selected from the group consisting of O, S, SO, $SO_2$ and NH, a loweralkylene or 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 triene of the following formula 4:




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;

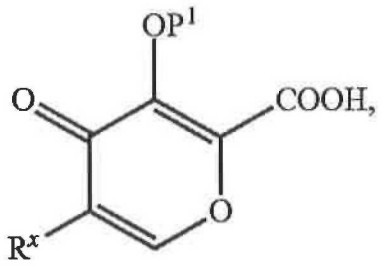
X is a single bond, a heteroatom group selected from the group consisting of O, S, SO, $SO_2$ and NH, a loweralkylene or lowerlalkylene a loweralkylene wherein each alkyl may be intervened by a heteroatom;

$R^2$ is optionally substituted aryl;

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,



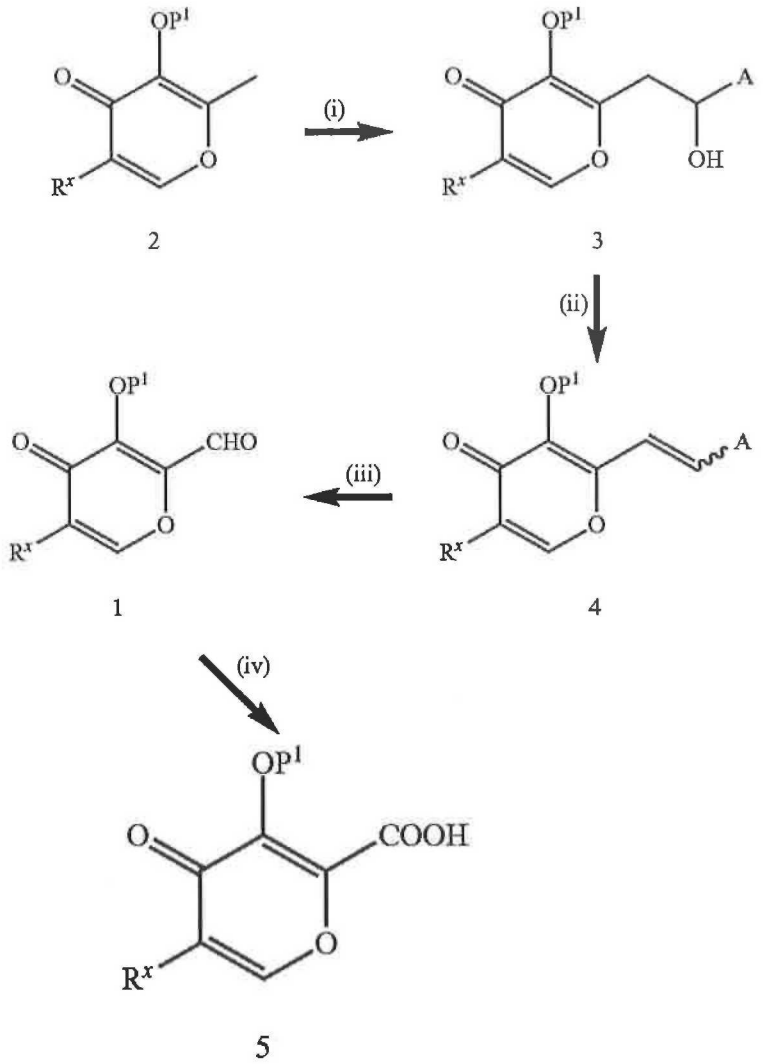

which comprises the steps of:

(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:

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

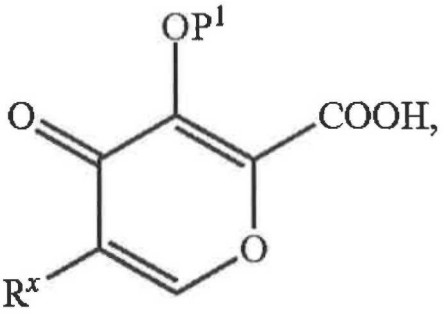
$R^1$ is hydrogen or lower alkyl;

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.

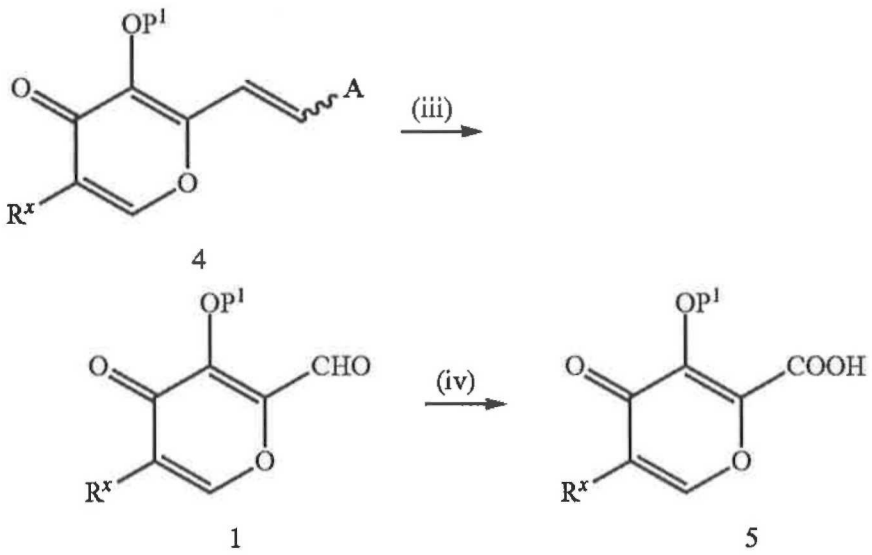
In another aspect, there is provided a process of producing a carboxylic acid of formula 5,



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:

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

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

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

$R^2$ 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: