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(54) **PROCESS FOR STEREOSELECTIVE SYNTHESIS OF PROSTACYCLIN DERIVATIVES**

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(62) Division of application No. 09/541,521, filed on Apr. 3, 2000, now Pat. No. 6,441,245, which is a continuation-in-part of application No. 09/481,390, filed on Jan. 12, 2000, now abandoned, which is a continuation of application No. 08/957,736, filed on Oct. 24, 1997, now abandoned.

(51) **Int. Cl.**[7] **C07C 37/00**; C07C 33/34

(52) **U.S. Cl.** **568/806**; 568/807

(58) **Field of Search** 568/379, 338, 568/311, 316, 322, 327, 807, 806, 632, 633, 634, 715; 560/56, 121, 503

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(57) **ABSTRACT**

An improved method is described for making 9-deoxy-PGF_1-type compounds. In contrast to the prior art, the method is stereoselective and requires fewer steps than the known methods for making these compounds. The invention also relates to novel intermediates prepared during the synthesis of the 9-deoxy-PGF_1-type compounds.

4 Claims, No Drawings

PROCESS FOR STEREOSELECTIVE SYNTHESIS OF PROSTACYCLIN DERIVATIVES

This application is a divisional of U.S. patent application Ser. No. 09/541,521, filed Apr. 3, 2000, now U.S. Pat. No. 6,441,245, which is a continuation-in-part of U.S. patent application Ser. No. 09/481,390, filed Jan. 12, 2000, now abandoned, which is a continuation of U.S. patent application Ser. No. 08/957,736, filed Oct. 24, 1997, now abandoned.

FIELD OF THE INVENTION

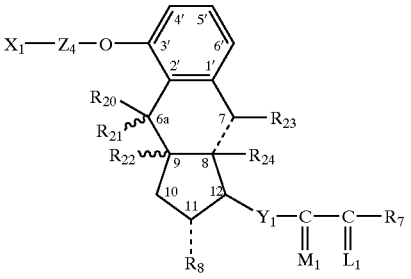
The present application relates to a process for producing prostacyclin derivatives and novel intermediate compounds useful in the process.

BACKGROUND OF THE INVENTION

Prostacyclin derivatives are useful pharmaceutical compounds possessing activities such as platelet aggregation inhibition, gastric secretion reduction, lesion inhibition, and bronchodilation.

For convenience, the novel prostacyclin derivatives will be referred to by the trivial, art-recognized system of nomenclature described by N. A. Nelson, J. Med. Chem. 17:911 (1974) for prostaglandins. Accordingly, all of the novel prostacyclin derivatives herein will be named as 9-deoxy-PGF_1-type compounds.

The prostacyclin derivatives prepared by the method disclosed in the '075 patent are as follows:



wherein L_1 is α-R_3:β-R_4, α-R_4: β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4: β-R_3, wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro;

wherein M_1 is α-OH: β-R_5 or α-R_5: β-OH, wherein R_5 is hydrogen or methyl;

wherein R_7 is

(1) -C_mH_{2m}-CH_3, wherein m is an integer from one to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1-C_3)alkyl, or

(4) cis—CH=CH-CH_2-CH_3,

(5) $(CH_2)_2$-CH(OH)-CH_3, or

(6) -$(CH_2)_3$—CH=C$(CH_3)_2$;

wherein -C(L_2)-R_7 taken together is

(1) (C_4-C_7)cycloalkyl optionally substituted by one to 3 (C_1-C_5) alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3thienyl)ethoxy, or

(4) 3-thienyloxymethyl;

wherein R_8 is hydroxy, hydroxymethyl, or hydrogen;

wherein

(1) R_{20}, R_{21}, R_{22}, R_{23}, and R_{24} are all hydrogen with R_{22} being either α-hydrogen or β-hydrogen,

(2) R_{20} is hydrogen, R_{21} and R_{22} taken together form a second valence bond between C-9 and C-6*a*, and R_{23} taken together form a second valence bond between C-8 and C-9 or are both kydrogen, or

(3) R_{22}, R_{23}, and R_{24} are all hydrogen, with R_{22} being either α-hydrogen or β-hydrogen, and

(a) R_{20} and R_{21} taken together are oxo, or

(b) R_{20} is kydrogen and R_{21} is hydroxy, being α-hydroxy or β-hydroxy;

wherein X_1 is

(1) -$COOR_1$, wherein R_1 is

(a) hydrogen,

(b) (C_1-C_{12})alkyl,

(c) (C_3-C_{10})cycloalkyl,

(d) (C_6-C_{12})aralkyl,

(e) phenyl, optionally substituted with one, 2 or 3 chloro or (C_1-C_1)alkyl,

(f) phenyl substituted in the para position by

(i) -NH-CO-R_{25},

(ii) -CO-R_{26},

(iii) -O-CO-R_{54}, or

(iv) -CH=N-NH-CO-NH_2 wherein R_{25} is methyl, phenyl, acetamidophenyl, benzamidophenyl, or -NH_2: R_{26} is methyl, phenyl, -NH_2, or methoxy; and R_{54} is phenyl or acetamidophenyl; inclusive, or

(g) a pharmacologically acceptiable cation;

(2) -CH_2OH,

(3) -COL_4, wherein L_4 is

(a) amino of the formula - - $NR_{51}R_{52}$, wherein R_{51} and R_{52} are

(i) hydrogen,

(ii) (C_1- C_{12})alkyl,

(iii) (C_3-C_{10})cycloalkyl,

(iv) (C_7- C_{12})aralkyl,

(v) phenyl, optionally substituted with one, 2 or 3 chloro, (C_1-C_3)alkyl, hydroxy, carboxy, (C_2-C_5) alkoxycarbonyl, or nitro,

(vi) (C_2-C_5)carboxyalkyl,

(vii) (C_2-C_5)carbamoylalkyl,

(viii) (C_2-C_5)cyanoalkyl,

(ix) (C_3-C_6)acetylalkyl,

(x) (C_7-C_{11})benzoalkyl, optionally substituted by oe, 2 or 3 chloro, (C_1-C_3)alkyl, hydroxy, (C_1-C_3) alkoxy, carboxy, (C_2-C_5)alkoxycarbonyl, or nitro,

(xi) pyridyl, optionally substituted by one, 2 or 3 chloro, (C_1-C_3)alkyl, or (C_1-C_3)alkoxy,

(xii) (C_6-C_9)pyridylalkyl optionally substituted by one, 2 or 3 chloro, (C_1-C_3)alkyl, hydroxy, or

(xiv) (C_1-C_4)dihydroxyalkyl,
(xv) (C_1-C_4)trihydroxyalkyl,

with the further proviso that not more than one of R_{51} and R_{52} is other than hydrogen or alkyl,

(b) cycloamino selected from the group consisting of lyrolidino, piperidino, morpholino, piperazino, hexamethyleneimino, pyrrolino, or 3,4-didehydropiperidinyl optionally substituted by one or 2 (C_1-C_{12})alkyl of one to 12 carbon atoms, inclusive,

(c) carbonylamino of the formula $-NR_{53}COR_{51}$, wherein R_{53} is hydrogen or (C_1-C_4)alkyl and R_{51} is other than hydrogen, but otherwise as defined above,

(d) sulfonylamino of the formula $-NR_{53}SO_2R_{51}$, wherein R_{51} and R_{53} are as defined in (c),

(4) $-CH_2NL_2L_3$, wherein L_2 and L_3 are kydrogen or (C_1-C_4)alkyl, being the same or different, or the pharmacologically acceptable acid addition salts thereof when X_1 is $-CH_2NL_2L_3$,

wherein Y_1 is trans-CH=CH-, cis-CH=CH-, CH_2CH_2-, or -C≡C-; and

wherein Z_4 is $-CH_2$- or $-(CH_2)$-CF_2, wherein f is zero, one, 2 or 3.

When X_1 is $-COOR_1$ of the Formulac in the '075 patent, the novel compounds so described are used for the purposes described and are in free acid form, in ester form, or in pharmacologically acceptable salt form. When the ester form is used, the ester is any of those within the above definition of R_1. However, it is preferred that the ester be alkyl of one to 12 carbon atoms, inclusive. Of the alkyl esters, methyl and ethyl are especially preferred for optimum absorption of the compound by the body or experimental animal system; and straight-chain oxtyl, nonyl, decyl, undecyl, and dodecyl are especially preferred for prolonged activity.

Pharmacologically acceptable salts of the novel prostaglandin analogs of this invention for the purposes described are those with pharmacologically acceptiable metal cations, ammonia, amine cations, or quaternary ammonium cations.

Especially preferred metal cations are those derived from the alkali metals, e.g., lithium, sodium, and potassium, and from the alkaline earth metals, e.g., magnesium and calcium, although cationic forms of other metals, e.g., aluminum, zinc, and iron are within the scope of this invention.

Pharmacologically acceptable amine cations are those derived from primary, secondary, and tertiary amines. Example of suitable amines are methylamine, dimethylamine, trimethylamine, ethylamine, dibutylamine, triisopropylamine, N-methylhexylamine, decylamine, dodecylamine, allylamine, crotylamine, cyclopentylamine, dicyclohexylamine, benzylamine, dibenzylamine, α-phenylethylamine, β-phenylethylamine, ethylenediamine, diethylenetriamine, adamantylamine, and the like aliphatic, cycloaliphatic, araliphatic amines containing up to and including about 18 carbon atoms, as well as heterocyclic amines, e.g., piperidine, morpholine, pyrrolidine, piperazie, and lower-alkyl derivatives thereto, e.g., 1-methylpiperidine, 4-ethylmorpholine, 1-isopropylpyrrolidine, 2-methylpyrrolidine, 1,4-dimethylpiperazine, 2-methylpiperidine, and the like as well ethyldiethanolamine, N-butylethanolamine, 2-amino-1-butanol, 2-amino-2-ethyl,-1,3-propanediol, 2-amino-2-methyl-1-propanol, tris(hydroxymethyl) aminomethane, N-phenylethanolamine, N-(p-tert-amylphenyl)-diethanolamine, galactamine, N-methylglycamine, N-methylglucosamine, ephedrine, phenylephrine, epinephrie, procaine, and the like. Further useful amine salts of the basic amino acid salt, e.g., lysie and arginine.

Examples of suitable pharmacologically acceptable quaternary ammonium cations are tetramethylammonium, tetraethylammonium, benzyltrimethylammonium, phenyltriethylammonium, and the like.

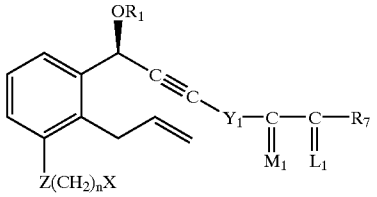
U.S. Pat. No. 4,306,075 discloses methods for making prostacyclin derivatives. However, these and other known processes involve a large number of steps. It is an object of the present invention to provide an improved method of preparing prostacyclin derivatives involving fewer steps.

SUMMARY OF THE INVENTION

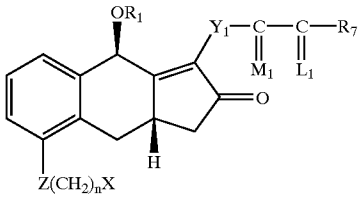
The present invention relates to a process for preparing 9-deoxy-PGF_1-type compounds by a process that is stereoselective and requires fewer steps than the prior art. The invention also relates to novel intermediates prepared during the synthesis of the 9-deoxy-PGF_1-type compounds.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In one embodiment, the present invention relates to an improved stereoselective method for making 9-deoxy-PGF_1-type compounds comprising converting a compound of the formula:



into a compound of the following formula:



wherein Z is O, S, CH_2, or NR_8 in which R_8 is H, alkyl or aryl;

X is H, CN, OR_9, or $COOR_9$ in which R_9 is alkyl, THP or TBDMS;

wherein n is 0, 1, 2, or 3;

wherein Y_1 is trans-CH═CH—, cis-CH═CH—, —CH_2

wherein R_7 is

(1) —C_pH_{2p}—CH_3, wherein p is an integer from one to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1–C_3)alkyl, or (C_1–C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1–C_3) alkyl, or (C_1–C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH═CH—CH_2—CH_3,

(5) —$(CH_2)_2$—CH(OH)—CH_3, or

(6) —$(CH_2)_3$—CH═$C(CH_3)_2$;

wherein —$C(L_1)$—R_7 taken together is

(1) (C_4–C_7)cycloalkyl optionally substituted by one to 3 (C_1–C_5) alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

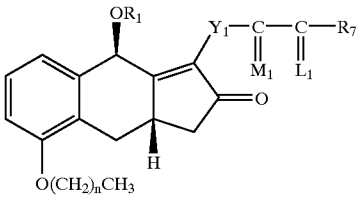
(4) 3-thienyloxymethyl;

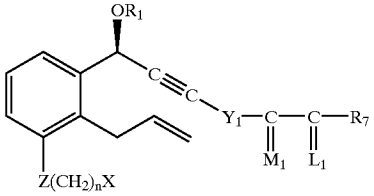
wherein M_1 is α-OH:β-R_5 or α-R_5:β-OH, wherein R_5 is hydrogen or methyl; and

wherein L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3,

wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

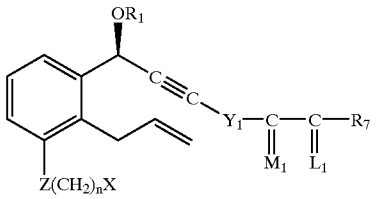
Preferably, the above conversion is carried out through cobalt-mediated cyclization, in which a complex is formed with the alkynyl group of the starting compound, which decomposes upon heating to form a tricyclic structure. More preferably, this cyclization is carried out by reacting $Co_2(CO)_8$ with the above compound of the formula:





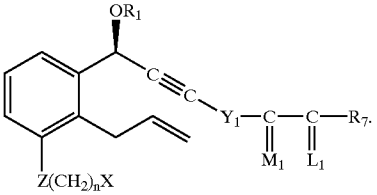
using a suitable non-reactive solvent. Preferably, the non-reactive solvent is a chlorinated solvent, a hydrocarbon solvent, or an aromatic solvent. More preferably, the non-reactive solvent is CH_2Cl_2, toluene, isooctane, and heptane.

In the case of carrying out the cobalt-mediated cyclization with CH_2Cl_2, after reacting $Co_2(CO)_8$ with the above compound of the formula:



in the presence of CH_2Cl_2 to form a complex with the alkynyl group, preferably the CH_2Cl_2 is removed in a subsequent step and replaced with CH_3CN followed by heating in an inert gas atmosphere, such as argon, nitrogen, or carbon monoxide, which decomposes the complex to form the above tricyclic compound.

Although $Co_2(CO)_8$ contributes a carbonyl during the reaction, it is not necessary to react equal amounts of the starting compound of the above formula and $Co_2(CO)_8$. It is also possible to use the $Co_2(CO)_8$ in a catalytic way, by introducing a relatively small amount of $Co_2(CO)_8$ and also introducing CO into the reaction mixture (e.g., by bubbling CO into the reaction mixture) in the presence of light which catalyzes the transfer of CO through a Co-mediated complex formed with the above compound of the formula:



In another preferred embodiment, the present invention relates to an improved stereoselective method for making 9-deoxy-PGF_1-type compounds comprising the following reaction:

wherein n is 0, 1, 2, or 3;

wherein Y_1 is trans-CH═CH—, cis-CH═CH—, —CH_2 $(CH_2)_m$—, or —C═C—; m is 1,2, or 3;

wherein R_1 is an alcohol protecting group;

wherein R_7 is

(1) —C_pH_{2p}—CH_3, wherein p is an integer from one to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C_1–C_3)alkyl, or

viso that R_7 is phenoxy or substituted phenoxy, only when R_3 and R_4 are hydrogen or methyl, being the same or different,

(3) phenyl, benzyl, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C_1–C_3) allyl, or (C_1–C_3)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH═CH—CH_2—CH_3,

(5) —$(CH_2)_2$—CH(OH)—CH_3, or

(6) —$(CH_2)_3$—CH═$C(CH_3)_2$;

wherein —$C(L_1)$—R_7 taken together is

(1) (C_4–C_7)cycloaklyl optionally substituted by one to 3 (C_1–C_5) alkyl;

(2) 2-(2-furyl)ethyl,

(3) 2-(3-thienyl)ethoxy, or

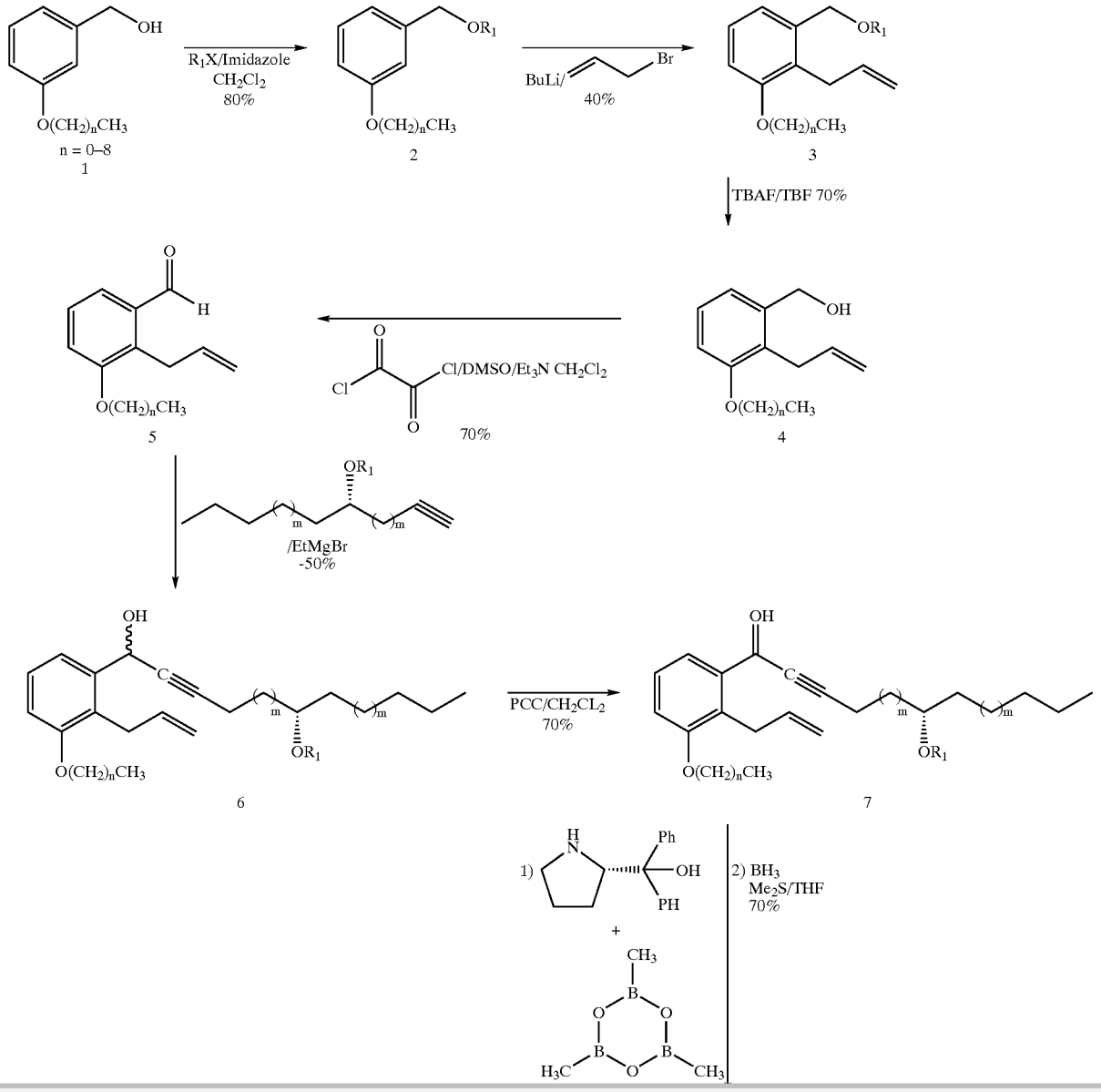
(4) 3-thienyloxymethyl;

wherein M_1 is α-OH:β-R_5 or α-R_5:β-OH, wherein R_5 is hydrogen or methyl;

wherein L_1 is α-R_3:β-R_4, α-R_4:β-R_3, or a mixture of α-R_3:β-R_4 and α-R_4:β-R_3,

wherein R_3 and R_4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R_3 and R_4 is fluoro only when the other is hydrogen or fluoro.

The present invention also relates to a method of making the following compounds utilizing the foregoing reaction:



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