



US006765117B2

(12) **United States Patent**
Moriarty et al.

(10) **Patent No.:** **US 6,765,117 B2**
(45) **Date of Patent:** **Jul. 20, 2004**

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

(75) Inventors: **Robert M. Moriarty**, Oak Park, IL (US); **Raju Penmasta**, Bolingbrook, IL (US); **Liang Guo**, Chicago, IL (US); **Munagala S. Rao**, Westmont, IL (US); **James P. Staszewski**, Naperville, IL (US)

(73) Assignee: **United Therapeutic Corporation**, Washington, DC (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **10/184,907**

(22) Filed: **Jul. 1, 2002**

(65) **Prior Publication Data**

US 2002/0173672 A1 Nov. 21, 2002

Related U.S. Application Data

(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

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,306,075 A 12/1981 Aristoff
5,153,222 A 10/1992 Tadepalli et al.

FOREIGN PATENT DOCUMENTS

EP 0087237 8/1983
WO 98/39337 9/1998

OTHER PUBLICATIONS

J. J. F. Belch et al., "Randomized, Double-Blind, Placebo-Controlled Study Evaluating the Efficacy and Safety of AS-013, a Prostaglandin EI Prodrug, in Patients with Intermittent Claudication," *Circulation*, vol. 95, No. 9, pp. 2298-2302 (1997).

N. A. Nelson, "Prostaglandin Nomenclature," *Journal of Medicinal Chemistry*, vol. 17, No. 9, pp. 911-918 (1974).

S. Takano et al., "Enantiodivergent Synthesis of Both Enantiomers of Sulcatol and Matsutake Alcohol from @-Epichlorohydrin," *Chemistry Letters*, pp. 2017-2020 (1987).

D. J. Mathre et al., "A Practical Enantioselective Synthesis of α,ϵ -Diaryl-2-pyrrolidinemethanol, Preparation and Chemistry of the Corresponding Oxazaborolidines," *J. Org. Chem.*, vol. 56, pp. 762-762, (1991).

B. L. Pagenkoph, "Substrate and Reagent Control of Diastereoselectivity in Transition Metal-Mediated Process: Development of a Catalytic Photo Promoted Pauson-Khand Reaction," *Diss. Abstr. Int.*, vol. 57, No. 12, p. 7535 (1997) Abstract XP-002097925.

J. Mulzer et al., "Asymmetric Synthesis of Carbacyclin Precursors by Pauson-Khand Cyclization," *Liebigs Ann. Chem.*, vol. 9, pp. 891-897 (1988) Abstract XP-002097924.

I. U. Khand et al., "Organocobalt Complexes. Part II. Reaction of Acetylenehexacarbonyldicobalt Complexes, (R1C2R2)Co2(CO)6, with Norbornene and its Derivatives," *J. Chem. Soc. Perkin Trans.*, pp. 977-981, (1973).

P. L. Pauson, "A Convenient and General Route to a Wide Range of Cyclopentenone Derivatives," *Tetrahedron*, vol. 41, No. 24, pp. 5855-5860 (1985).

N. E. Schore, "Transition-Metal-Mediated Cycloaddition Reactions of Alkynes in Organic Synthesis," *Chem. Rev.*, vol. 88, pp. 1081-1119 (1988).

S. Shambayati et al., "N-Oxide Promoted Pauson-Khand Cyclizations at Room Temperature," *Tetrahedron Letters*, vol. 31, pp. 5289-5292 (1990).

V. K. Chung et al., "Promoters for the (Alkyne)hexacarbonyldicobalt-Based Cyclopentenone Synthesis," *Organometallics*, vol. 12, pp. 220-223 (1993).

N. Jeong et al., "Catalytic Version of the Intramolecular Pauson-Khand Reaction," *J. Am. Chem. Soc.*, vol. 116, pp. 3159-3160 (1994).

F. A. Hicks et al., "A Practical Titanium-Catalyzed Synthesis of Bicyclic A17 Cyclopentenones and Allylic Amines," *J. Org. Chem.*, vol. 61, pp. 2713-2718 (1996).

M. Zhang et al., "A Nickel(O)-Catalyzed Process for the Transformation of Enynes to Bicyclic Cyclopentenones," *J. Org. Chem.*, vol. 61, pp. 4498-4499 (1996).

B. L. Pagenkopf et al., "Photochemical Promotion of the Intramolecular Pauson-Khand Reaction. A New Experimental Protocol for Cobalt-Catalyzed [2+2+11] Cycloadditions," *J. Am. Chem. Soc.*, vol. 118, pp. 2285-2286 (1996).

Primary Examiner—James O. Wilson

Assistant Examiner—Sikarl A. Witherspoon

(74) *Attorney, Agent, or Firm*—Foley & Lardner LLP

(57) **ABSTRACT**

An improved method is described for making 9-deoxy-PGF₁-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-PGF₁-type compounds.

4 Claims, No Drawings

1

**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

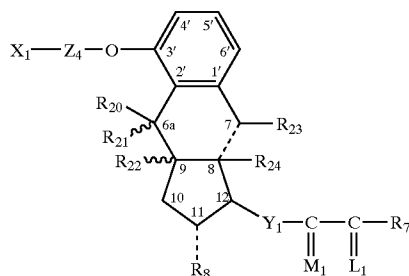
The present application relates to a process for producing prostacyclin derivatives and novel intermediate compounds useful in the process.

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-PGF₁-type compounds.

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



wherein L₁ is α-R₃:β-R₄, α-R₄:β-R₃, or a mixture of α-R₃:β-R₄ and α-R₄:β-R₃, wherein R₃ and R₄ are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R₃ and R₄ is fluoro only when the other is hydrogen or fluoro;

wherein M₁ is α-OH:β-R₅ or α-R₅:β-OH, wherein R₅ is hydrogen or methyl;

wherein R₇ is

- (1) -C_mH_{2m}-CH₃, wherein m is an integer from one to 5, inclusive,
- (2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C₁-C₃)alkyl, or (C₁-C₃)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R₇ is phenoxy or substituted phenoxy, only when R₃ and R₄ 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, (C₁-C₃)alkyl, or

2

- (4) cis-CH=CH-CH₂-CH₃,
- (5) (CH₂)₂-CH(OH)-CH₃, or
- (6) -(CH₂)₃-CH=C(CH₃)₂;

wherein -C(L₂)-R₇ taken together is

- (1) (C₄-C₇)cycloalkyl optionally substituted by one to 3 (C₁-C₅) alkyl;
- (2) 2-(2-furyl)ethyl,
- (3) 2-(3-thienyl)ethoxy, or
- (4) 3-thienyloxymethyl;

wherein R₈ is hydroxy, hydroxymethyl, or hydrogen; wherein

- (1) R₂₀, R₂₁, R₂₂, R₂₃, and R₂₄ are all hydrogen with R₂₂ being either α-hydrogen or β-hydrogen,
- (2) R₂₀ is hydrogen, R₂₁ and R₂₂ taken together form a second valence bond between C-9 and C-6a, and R₂₃ taken together form a second valence bond between C-8 and C-9 or are both hydrogen, or
- (3) R₂₂, R₂₃, and R₂₄ are all hydrogen, with R₂₂ being either α-hydrogen or β-hydrogen, and
 - (a) R₂₀ and R₂₁ taken together are oxo, or
 - (b) R₂₀ is hydrogen and R₂₁ is hydroxy, being α-hydroxy or β-hydroxy;

wherein X₁ is

- (1) -COOR₁, wherein R₁ is
 - (a) hydrogen,
 - (b) (C₁-C₁₂)alkyl,
 - (c) (C₃-C₁₀)cycloalkyl,
 - (d) (C₆-C₁₂)aralkyl,
 - (e) phenyl, optionally substituted with one, 2 or 3 chloro or (C₁-C₁)alkyl,
 - (f) phenyl substituted in the para position by
 - (i) -NH-CO-R₂₅,
 - (ii) -CO-R₂₆,
 - (iii) -O-CO-R₅₄, or
 - (iv) -CH=N-NH-CO-NH₂ wherein R₂₅ is methyl, phenyl, acetamidophenyl, benzamidophenyl, or -NH₂; R₂₆ is methyl, phenyl, -NH₂, or methoxy; and R₅₄ is phenyl or acetamidophenyl; inclusive, or
 - (g) a pharmacologically acceptable cation;

(2) -CH₂OH,

(3) -COL₄, wherein L₄ is

- (a) amino of the formula -NR₅₁R₅₂, wherein R₅₁ and R₅₂ are
 - (i) hydrogen,
 - (ii) (C₁-C₁₂)alkyl,
 - (iii) (C₃-C₁₀)cycloalkyl,
 - (iv) (C₇-C₁₂)aralkyl,
 - (v) phenyl, optionally substituted with one, 2 or 3 chloro, (C₁-C₃)alkyl, hydroxy, carboxy, (C₂-C₅)alkoxycarbonyl, or nitro,
 - (vi) (C₂-C₅)carboxyalkyl,
 - (vii) (C₂-C₅)carbamoylalkyl,
 - (viii) (C₂-C₅)cyanoalkyl,
 - (ix) (C₃-C₆)acetylalkyl,
 - (x) (C₇-C₁₁)benzoalkyl, optionally substituted by one, 2 or 3 chloro, (C₁-C₃)alkyl, hydroxy, (C₁-C₃)alkoxy, carboxy, (C₂-C₅)alkoxycarbonyl, or nitro,
 - (xi) pyridyl, optionally substituted by one, 2 or 3 chloro, (C₁-C₃)alkyl, or (C₁-C₃)alkoxy,
 - (xii) (C₆-C₉)pyridylalkyl optionally substituted by one, 2 or 3 chloro, (C₁-C₃)alkyl, hydroxy, or

3

(xiv) (C₁-C₄)dihydroxyalkyl,(xv) (C₁-C₄)trihydroxyalkyl,

with the further proviso that not more than one of R₅₁ and R₅₂ 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 (C₁-C₁₂)alkyl of one to 12 carbon atoms, inclusive,

(c) carbonylamino of the formula -NR₅₃COR₅₁, wherein R₅₃ is hydrogen or (C₁-C₄)alkyl and R₅₁ is other than hydrogen, but otherwise as defined above,

(d) sulfonylamino of the formula -NR₅₃SO₂R₅₁, wherein R₅₁ and R₅₃ are as defined in (c),

(4) -CH₂NL₂L₃, wherein L₂ and L₃ are hydrogen or (C₁-C₄)alkyl, being the same or different, or the pharmacologically acceptable acid addition salts thereof when X₁ is -CH₂NL₂L₃,

wherein Y₁ is trans-CH=CH-, cis-CH=CH-, CH₂CH₂-, or -C≡C-; and

wherein Z₄ is -CH₂- or -(CH₂)-CF₂, wherein f is zero, one, 2 or 3.

When X₁ is -COOR₁ 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 R₁. 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 octyl, 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 acceptable 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, piperazine, 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

4

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-amyphenyl)-diethanolamine, galactamine, N-methylglycamine, N-methylglucosamine, ephedrine, phenylephrine, epinephrine, procaine, and the like. Further useful amine salts of the basic amino acid salt, e.g., lysine and arginine.

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

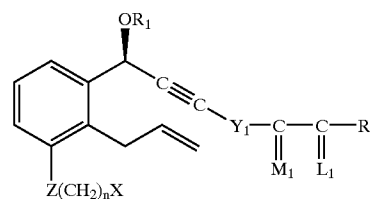
U.S. Pat. No. 4,306,075 discloses methods for making prostacyclin derivatives. However, these and other known processes involve a large number of steps. It is an object of the present invention to provide an improved method of preparing prostacyclin derivatives involving fewer steps.

SUMMARY OF THE INVENTION

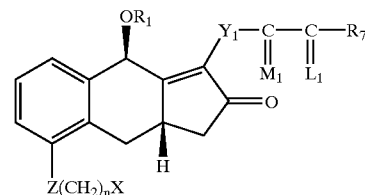
The present invention relates to a process for preparing 9-deoxy-PGF₁-type compounds by a process that is stereoselective and requires fewer steps than the prior art. The invention also relates to novel intermediates prepared during the synthesis of the 9-deoxy-PGF₁-type compounds.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In one embodiment, the present invention relates to an improved stereoselective method for making 9-deoxy-PGF₁-type compounds comprising converting a compound of the formula:



into a compound of the following formula:



wherein Z is O, S, CH₂, or NR₈ in which R₈ is H, alkyl or aryl;

X is H, CN, OR₉, or COOR₉ in which R₉ is alkyl, THP or TBDMS;

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

wherein Y₁ is trans-CH=CH-, cis-CH=CH-, -CH₂(CH₂)_n- or -C≡C-; n is 1, 2, or 3;

5

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

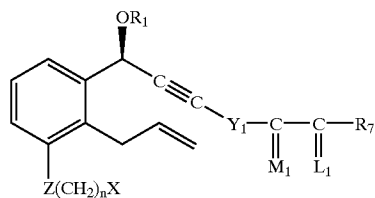
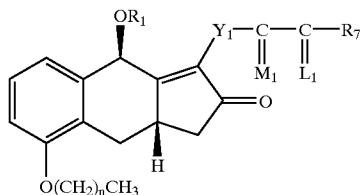
- (1) (C_4-C_7) cycloalkyl optionally substituted by one to 3 (C_1-C_5) alkyl;
- (2) 2-(2-furyl)ethyl,
- (3) 2-(3-thienyl)ethoxy, or
- (4) 3-thienyloxymethyl;

wherein M_1 is $\alpha-OH:\beta-R_5$ or $\alpha-R_5:\beta-OH$, wherein R_5 is hydrogen or methyl; and

wherein L_1 is $\alpha-R_3:\beta-R_4$, $\alpha-R_4:\beta-R_3$, or a mixture of $\alpha-R_3:\beta-R_4$ and $\alpha-R_4:\beta-R_3$,

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.

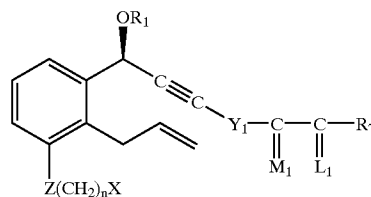
Preferably, the above conversion is carried out through cobalt-mediated cyclization, in which a complex is formed with the alkynyl group of the starting compound, which decomposes upon heating to form a tricyclic structure. More preferably, this cyclization is carried out by reacting $Co_2(CO)_8$ with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



6

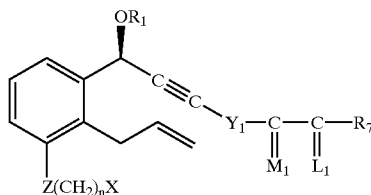
using a suitable non-reactive solvent. Preferably, the non-reactive solvent is a chlorinated solvent, a hydrocarbon solvent, or an aromatic solvent. More preferably, the non-reactive solvent is CH_2Cl_2 , toluene, isooctane, and heptane.

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:

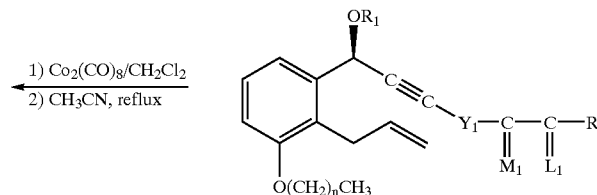


in the presence of CH_2Cl_2 to form a complex with the alkynyl group, preferably the CH_2Cl_2 is removed in a subsequent step and replaced with CH_3CN followed by heating in an inert gas atmosphere, such as argon, nitrogen, or carbon monoxide, which decomposes the complex to form the above tricyclic 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-PGF₁-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

7

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) $\text{cis-CH=CH-CH}_2\text{-CH}_3$,

(5) $\text{-(CH}_2\text{)}_2\text{-CH(OH)-CH}_3$, or

(6) $\text{-(CH}_2\text{)}_3\text{-CH=C(CH}_3\text{)}_2$;

wherein $\text{-(L}_1\text{)-R}_7$ taken together is

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

8

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

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

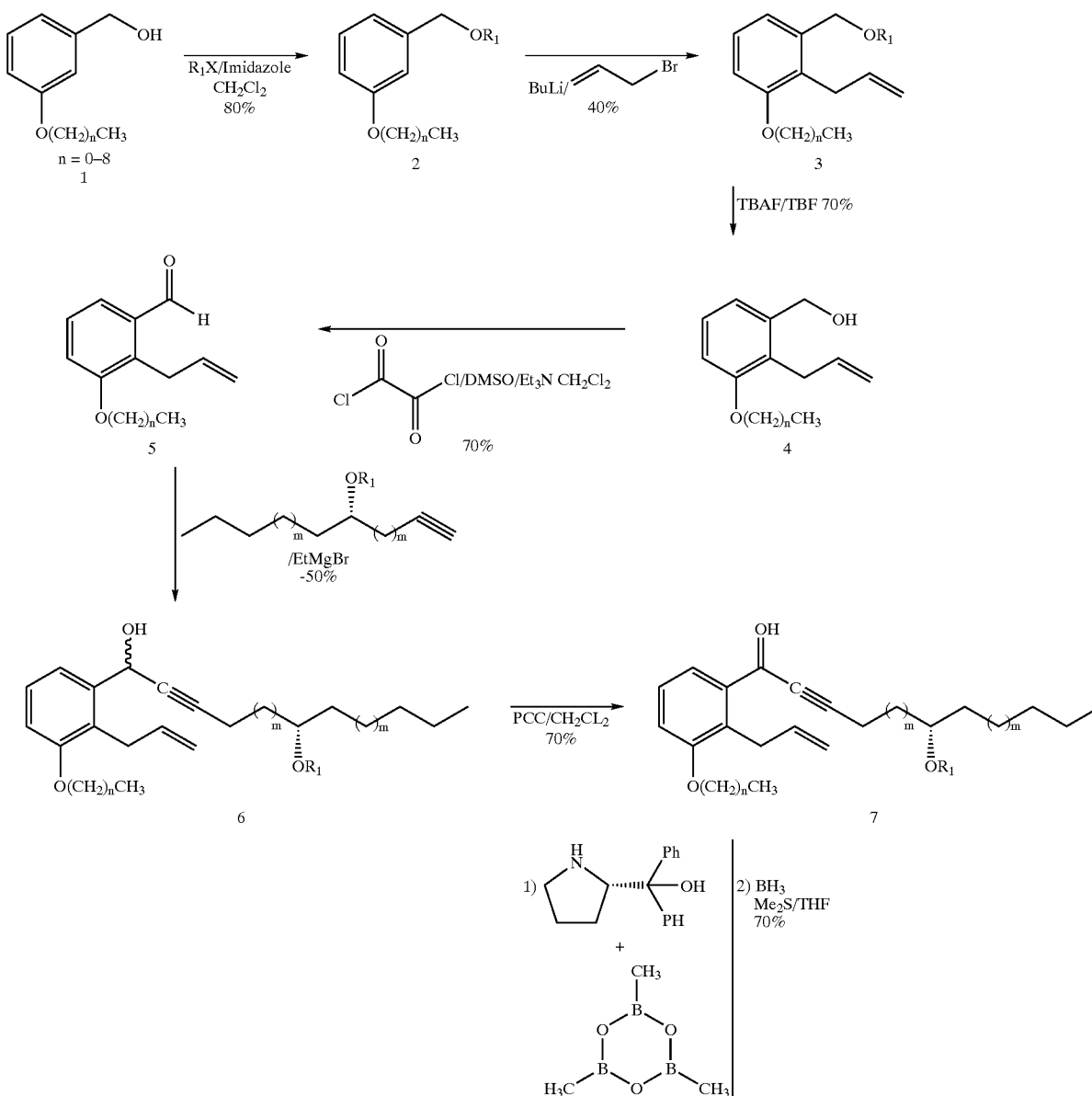
(4) 3-thienyloxymethyl;

wherein M_1 is $\alpha\text{-OH}:\beta\text{-R}_5$ or $\alpha\text{-R}_5:\beta\text{-OH}$, wherein R_5 is hydrogen or methyl;

wherein L_1 is $\alpha\text{-R}_3:\beta\text{-R}_4$, $\alpha\text{-R}_4:\beta\text{-R}_3$, or a mixture of $\alpha\text{-R}_3:\beta\text{-R}_4$ and $\alpha\text{-R}_4:\beta\text{-R}_3$,

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:



Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.