EXHIBIT B
PROCESS FOR STEREOSELECTIVE SYNTHESIS OF PROSTACYCLIN DERIVATIVES

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

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.

Appl. No.: 10/184,907
Filed: Jul. 1, 2002

Prior Publication Data
US 2002/0173672 A1 Nov. 21, 2002

Related U.S. Application Data
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. 09/957,736, filed on Oct. 24, 1997, now abandoned.

Int. Cl.7 C07C 37/00, C07C 33/34
U.S. Cl. 568/806, 568/807
Field of Search 568/379, 338, 568/311, 316, 322, 327, 807, 806, 632, 633, 634, 715; 560/56, 121, 503

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

OTHER PUBLICATIONS

Primary Examiner—James O. Wilson
Assistant Examiner—Sikaril A. Witherspoon
(74) Attorney, Agent, or Firm—Foley & Lardner LLP

ABSTRACT
An improved method is described for making 9-deoxy-PGF₁₂-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-PGF₁₂-type compounds.

4 Claims, No Drawings
PROCESS FOR STEREOSELECTIVE SYNTHESIS OF PROSTACYCLIN DERIVATIVES

This application is a division 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 prostanoid 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 prostanoid 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 prostanoids. Accordingly, all of the novel prostanoid derivatives herein will be named as 9-deoxy-PGF1α-type compounds.

The prostanoid derivatives prepared by the method disclosed in the ’075 patent are as follows:

wherein L1 is α-R1:β-R2: α-R3:β-R4 or a mixture of α-R1:β-R2 and α-R3:β-R4, wherein R2 and R4 are hydrogen, methyl, or fluoro, being the same or different, with the proviso that one of R1 and R3 is fluoro only when the other is hydrogen or fluoro; wherein M1 is α-OH:β-R4 or α-R4:β-OH, wherein R4 is hydrogen or methyl; wherein R3 is

1. -CmH2m-CH3, wherein m is an integer from one to 5, inclusive;
2. phenoxo optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C1-C6)alkyl, or (C1-C6)alk oxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that 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-C6)alkyl, or (C1-C6)alkoxy, with the proviso that not more than two substituents are other than alkyl.

(4) cis—CH=CH-CH2-CH3,
(5) (CH2)n-CH(OM)-CH3, or
(6) -CH=CH=C(CH3)2,
wherein -(L2)-R4 taken together is
1. (C4-C8)cycloalkyl optionally substituted by one to 3 (C1-C6)alkyl;
2. 2-(2-furyl)ethyl,
3. 2-(3-thienyl)ethoxy, or
4. 3-thienylmethoxy;
wherein R8 is hydrogen, hydroxy, hydroxymethyl, or hydrogen;
wherein
1. R20, 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. with 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) (C2-C10)cycloalkyl,
(d) (C5-C12)arylalkyl,
(e) phenyl, optionally substituted with one, two or three chloro or (C1-C6)alkyl,
(f) phenyl substituted in the para position by
(i) -NH-CO-R25,
(ii) -CO-R26,
(iii) -O-CO-R26, or
(iv) -CH=N-NH-CO-NH2 wherein R25 is methyl, phenyl, acetamidophenyl, benzamidophenyl, or -NH2; R26 is methyl, phenyl, -NH2, or methoxy; and R27 is phenyl or acetamidophenyl; inclusive, or
(g) a pharmacologically acceptable cation;
2. -CH3OH,
3. -COL4, wherein L4 is
(a) amino of the formula -NR52R53, wherein R51 and R52 are
(i) hydrogen,
(ii) (C1-C6)alkyl,
(iii) (C3-C10)cycloalkyl,
(iv) (C1-C6)alkylacyl,
(v) phenyl, optionally substituted with one, two or three chloro, (C1-C6)alkyl, hydroxy, carboxy, (C2-C5)alkoxycarbonyl, or nitro,
(vi) (C2-C6)carboxyalkyl,
(vii) (C2-C6)carbamoylalkyl,
(viii) (C2-C5)cyanoalkyl,
(ix) (C3-C6)acylalkyl,
(x) (C2-C11)benzoalkyl, optionally substituted by one of 2, or 3 chloro, (C1-C6)alkyl, hydroxy, (C1-C6)alkoxycarbonyl, or nitro,
(xi) pyridyl, optionally substituted by one, two or three chloro, (C1-C6)alkyl, or (C1-C6)alkoxy,
(xii) (C6-C8)pyridylalkyl optionally substituted by one, or 2, or 3 chloro, (C1-C6)alkyl, or (C1-C6)alkoxy,
(xiii) (C1-C6)hydroxyalkyl,
US 6,765,117 B2

3
(xiv) (C₂₋C₆)₆dihydroxyalkyl,
(xv) (C₂₋C₆)₆threohydroxyalkyl,
with the further proviso that not more than one of R₁⁺ and R₂ is other than hydrogen or alkyl,
(b) cycloaminos selected from the group consisting of
lylolidino, piperidino, morpholino, piperazino,
hexamethyleneimino, pyrrolino, or 3,4-
dihydrodropiperidinyl optionally substituted by one or two (C₁₋C₆)₆alkyl of one to 12 carbon atoms, inclusive,
(c) carbonylmino of the formula -NR₅₋₅COR₅₋₅,
wherein R₅₋₅ is hydrogen or (C₁₋C₆)₆alkyl and R₅₋₅ is other than hydrogen, but otherwise as defined above,
(d) sulfonamido of the formula -NR₅₋₅SO₂R₅₋₅,
wherein R₅₋₅ and R₅₋₅ are as defined in (c).
(4) -CH₃NL₃₋₃, wherein L₁ and L₃ are hydrogen or (C₁₋C₆)₆alkyl, being the same or different, or the pharmaceutically acceptable acid addition salts thereof
when X₁ is -CH₂NL₃₋₃,
wherein Y₁ is -trans-CH=CH₂, cis-CH=CH₂, CH₂CH₂-, or
-C₆H₅ and
wherein Z₁ is -CH₂- or -(CH₂)ₓCFₓ₂, wherein f is zero, one, two or three.
When X₁ is -COOR₁, of the Formula 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 pharmaceutically 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 oxlyl, 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 pharmaceutically acceptable metal cations, ammonia, amine cations, or quaternary ammonium cations.
Especially preferred metal cations are those derived from the alkaline 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, trisopropylamine, N-methylethylamine, decylamine, dodecylamine, allylamine, crotylamine, cyclopentylamine, dicyclohexylamine, benzylamine, dibenzylamine, α-phenylethylamine, β-phenylethylamine, ethylenediamine, diethylenetriamine, adamantylamine, and the like aliphatic, cycloaliphatic, alicyclic amines containing up to and including about 18 carbon atoms, as well as heterocyclic amines, e.g., piperidine, morpholine, pyrrolidine, piperazin, and lower-alkyl derivatives thereof, e.g., 1-methylpiperidine, 4-ethylmorpholine, 1-isopropylpyrrolidine, 2-methylpyrrolidine, 1,4-dimethylpiperazin, 2-methylpiperidine, and the like as well as amines containing water-solubilizing or hydrophilic groups, e.g., mono-, di-, and triethanolamine,
ethyldiethanolamine, N-butylethanolamine, 2-amino-1-
butanol, 2-amino-2-ethyl-1,3-propanediol, 2-amino-2-
methyl-1-propanol, (trans-hydroxymethyl) aminomethane, N-phenylethanolamine, N-(p-tert-amylpheryl)-
diethanolamine, galactamine, N-methylglycamin, N-methylglucosamin, ephedrine, phenylephrine, epinephrin, procaine, and the like. Further useful amine salts of the basic amino acid salt, e.g., lysine and arginine.
Examples of suitable pharmaceutically acceptable qua-
ternary ammonium cations are tetramethylammonium, tetraethylammonium, benzyltrimethylammonium, phenyltrimethylammonium, 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-PGF₁₁-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-PGF₁₁-type compounds.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

In one embodiment, the present invention relates to an improved stereoselective method for making 9-deoxy-
PGF₁₁-type compounds comprising converting a compound of the formula:

![Chemical Structure 1](image1)

into a compound of the following formula:

![Chemical Structure 2](image2)

wherein Z is O, S, CH₅, or NR₉, in which R₉ 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=CH₂, cis-CH=CH₂, =CH₂
(CH₂)ₓ, or =C≡C--; m is 1, 2, or 3;
wherein R₂ is an alcohol protecting group;
wherein R₂ is
(1) —C₉H₂₉—CH₃, wherein p is an integer from one to 5, inclusive,
(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C₁₋C₅)alkyl, or (C₁₋C₅)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R₁ 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₋C₅)alkyl, or (C₁₋C₅)alkoxy, with the proviso that not more than two substituents are other than alkyl,
(4) cis-CH=CH—CH₃,
(5) —(CH₂)₄—CH(OH)—CH₃, or
(6) —(CH₂)₅—CH=CH(CH₃)₂;
wherein —C(L)₉—R₃ taken together is
(1) (C₁₋C₅)cycloalkyl optionally substituted by one to 5 (C₁₋C₅)alkyl,
(2) 2-(2-furyl)ethyl,
(3) 2-(3-thienyl)ethoxy, or
(4) 3-thienoxy1-methyl;
wherein M₁ is α-OH:β-R₅ or α-R₆:β-OH, wherein R₆ is hydrogen or methyl; and
wherein L₁ is α-R₇:β-R₆, α-R₇:β-R₈, or a mixture of α-R₇:β-R₆ and α-R₇:β-R₈,
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.

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 Co₂(CO)₉ with the above compound of the formula:

US 6,765,117 B2

In another preferred embodiment, the present invention relates to an improved stereoselective method for making 9-deoxy-PGF₁α-type compounds comprising the following reaction:

wherein n is 0, 1, 2, or 3;
wherein Y₁ is trans-CH=CH—, cis-CH=CH—, —CH₂(CH₂)₄—, or —C≡C—; m is 1, 2, or 3;
wherein R₄ is an alcohol protecting group;
wherein R₅ is
(1) —C₉H₂₉—CH₃, wherein p is an integer from one to 5, inclusive,
(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C₁₋C₅)alkyl, or (C₁₋C₅)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the pro-
visor that $R_3$ 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=CH$_2$, (5) ($CH_2$)$_2$-CH(OH)-CH$_2$, or (6) ($CH_2$)$_3$-CH=CH($CH_2$)$_2$; wherein $-(C=O)$-$R_5$ taken together is (1) ($C_1$-$C_3$)cycloalkyl optionally substituted by one to 3 ($C_1$-$C_3$) alkyl; (2) 2-(2-furyl)ethyl, (3) 2-(3-thiényl)ethoxy, or (4) 3-thienylmethoxy. wherein $R_1$ is $\alpha$-$OH$; $\beta$-$R_5$ or $\alpha$-$R_5$-$\beta$-$OH$, wherein $R_5$ is hydrogen or methyl, wherein $L_1$ is $\alpha$-$R_3$-$\beta$-$R_4$, $\alpha$-$R_4$-$\beta$-$R_5$, or a mixture of $\alpha$-$R_3$-$\beta$-$R_4$ and $\alpha$-$R_4$-$\beta$-$R_5$, 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:
wherein $R_1$ is in each case an independently selected alcohol protecting group. Preferred alcohol protecting groups are tertiary butyl dimethyl silyl (TBDMS) and tetra hydro pyranyl (THP).

The present invention also relates to the following novel intermediate compounds:

![Chemical structures](image)

wherein $X$, $Y$, $Z$, $M_1$, $M_2$, $L_1$, $L_2$, $R_1$, and $R_2$ are as defined above.

The present invention is further illustrated by, though in no way limited to, the following examples.

**EXAMPLE 1**

9-Deoxy-2',9α-methano-3-oxa4,5,6-trinor-3,7-(1',3'-inter-phenylene)-13,14-dihydro-PGF$_2$-

![Chemical structures](image)

To a solution of 95 g (376 mmol) of 2 dissolved in 400 ml of hexane under Ar at room temperature were added drop-wise 26.5 g (414 mmol, 1.1 eq.) of BuLi in 166 ml of hexane. The mixture was stirred for 2 hours at room temperature, and then the reaction was cooled in an ice bath and 54.6 g (452 mmol) of allyl bromide were added drop-wise. The reaction was allowed to warm to room temperature overnight. After stirring for 24 hours, TLC indicated 60% conversion, and the reaction was quenched with saturated NH$_3$Cl. The organic layer was separated and washed with Brine, dried over MgSO$_4$, and filtered. Evaporation of the solvent yielded a yellow oil which was used in the next reaction without further purification.
Procedure

To a solution of 20.6 g (162 mmol, 1.2 eq.) of oxalyl chloride in 250 ml of CH₂Cl₂ under Ar at −78°C, were added dropwise 24.2 g (310 mmol) of DMSO in 100 ml of CH₂Cl₂. After 10 minutes, 24 g (135 mmol) of 4 in 100 ml of CH₂Cl₂ were added dropwise. The mixture was stirred at −78°C for 30 min., and then 68.3 g (675 mmol, 5.0 eq.) of Et₃N were added. Stirring continued as the reaction warmed to room temperature. The reaction was quenched with H₂O, washed with saturated NH₄Cl solution and Brine. The organic layer was separated and dried over MgSO₄. Filtration and evaporation of the solvent produced a brown oil which was purified by flash column chromatography, on silica gel using 10–30% ethyl acetate in hexanes as the eluent. The fractions containing the desired product were evaporated to afford 24 g (36% from 3-methoxybenzyl alcohol) of a yellow oil.
Case 3:12-cv-01617-PGS-LHG  Document 1-3  Filed 03/14/12  Page 10 of 14 PageID: 37

Compound A may be synthesized according to S. Takano et al., Chemistry Lett., 1987, p. 2017. To a solution of side chain (A) (1.6 g, 6.72 mmol) in dry THF (10 ml) which was heated to gentle refluxing under argon was added EtMgBr (2.24 ml, 6.72 mmol, 3M solution). After the addition was complete, the resultant solution was refluxed for 20 min.

The solution was cooled to 0°C. (under argon) and a solution of 5 (1.183 g, 6.72 mmol) in THF (10 ml) dried over molecular sieves was added dropwise with stirring. After the complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 2–3 hrs. The reaction mixture was cooled to 0°C., diluted with saturated NH₄Cl solution, concentrated, extracted with ethyl acetate (4×25 ml), dried (MgSO₄) and the solvent distilled off in vacuo. The crude product (2.65 g) was purified by flash chromatography using 10–30% ether in hexane on silica gel to obtain a colorless oil 1.45 g (52%) of 6.

**Procedure**

To a solution of alcohol 6 (1.27 g, 13.07 mmol) in dry CH₂Cl₂ (20 ml) was added pyridinium chlorochromate (PCC) (1.32 g, 6.12 mmol) and the mixture was stirred at room temperature. PCC slowly dissolved and the color of solution turned orange-black after approx. 5 min. Stirring was continued for 3 hrs. The reaction mixture was diluted with ether (100 ml) and filtered through a plug of silica gel. The solid was washed 3 times with ether (3×50 ml). After the solvent was removed, the crude product (1.3 g) was purified by flash chromatography using 10% ether in hexane on silica gel to give 900 mg light yellow oil (71%).

**STEP I: Preparation of Reagent:**

Compound B may be synthesized according to D. S. Mathre et al., J. Org. Chem. 1991, Vol. 56, p. 751; P. Beak, Org. Synth., 1997, p. 23. Compound B (1.08 g, 4.26 mmol) was dissolved in 30 ml of anh. toluene under argon. Trimethylboroxine (C) (0.357 g, 2.84 mmol) was added dropwise and the resulting solution was stirred at room temperature. White solid separated out after 3–4 min. After stirring for 30 min., toluene was distilled out at atmospheric pressure. Again 20 ml of dry toluene were added and distilled out. This distillation was repeated for 2 more times. The solution of reagent in toluene was allowed to cool under argon.

**STEP II: Reduction:**

A solution of ketone 7 (0.88 g, 2.14 mmol) in dry THF (20 ml) was dried over molecular sieves for 2 hrs and added to the above reagent solution. The resulting solution was cooled to -30°C. (CH₂CN, CO₂) under argon and borane-methylsulfoxide complex (1.07 ml, 10.71 mmol) was added dropwise with stirring. After stirring at -30°C for 1 hr, the reaction was quenched with methanol (10 ml), diluted with ether (100 ml), washed successively with saturated NH₄Cl, NaHCO₃ solution and brine, dried (MgSO₄) and concentrated in vacuo to yield a crude product (2.3 g). The crude product was purified by flash chromatography using 10% ether in hexanes on silica gel to give 770 mg of 8 as a colorless oil (87%).

**Procedure**

8 + TBDMSI + Imidazole → DMF

8 + TBDMSI (0.337 g, 2.23 mmol) and imidazole (0.335 g, 4.65 mmol) were added to the solution of 8 (0.770 g, 1.86
mmol) in DMF (20 ml) at room temperature under argon, and the mixture was stirred at room temperature for 3-4 hrs. After the reaction was quenched with sat. NH₄Cl, the reaction mixture was extracted with ether (3×50 ml). The combined ether extracts were dried (MgSO₄) and concentrated in vacuo. The crude oil was purified by chromatography using 5% ether in hexane on silica gel to yield 860 mg of 9 as a colorless oil (88%).

\[ \text{CH₃Cl₂} \quad \text{r.t., 30 min} \]
\[ \text{CH₃CN} \quad \text{reflux, 2 h} \]

Procedure

**STEP I: Complex formation:**

Compound 9 (0.840 g, 1.59 mmol) was dissolved in dry CH₃Cl₂ (15 ml) under argon, and CO₂(CO)₉ (0.653 g, 1.91 mmol) was added to it and stirred at room temperature under argon. Carbon monoxide evolved out slowly, and the solution turned dark brown after 5 min. Stirring was continued for 30 min. at room temperature.

**STEP II: Pauson Khand Cyclization**

CH₃Cl₂ was distilled out from the above solution. The complex was dissolved in dry CH₃CN (50 ml), and the solution was refluxed under argon for 2 hrs. This solvent was distilled out, the crude mass was dissolved in ether and passed quickly through a short column of neutral alumina to yield 850 mg of light brown oil (96%).

A solution of ketone 11 (0.430 g) in 95% ethanol was cooled to −10°C. 10% NaOH (6 ml) and NaBH₄ (0.080 g) were added and the mixture was stirred at −10°C for 1 hr. Then one more eq. of NaBH₄ (0.080 g) was added and stirring was continued for another 5 hrs. at −10°C. After quenching carefully with glacial acetic acid, the solvent was removed under reduced pressure. Resulting oil was distilled in ethyl acetate, washed with aq. NaHCO₃, brine, dried (MgSO₄) and concentrated in vacuo to obtain 430 mg of colorless oil (98%) which has a single spot on TLC. Further purification was not required.
19

Case 3:12-cv-01617-PGS-LHG Document 1-3 Filed 03/14/12 Page 12 of 14 PageID: 39

US 6,765,117 B2

TLC shows 80-90% conversion (14). The reaction mixture was cooled to -5°C and then an aqueous solution of NaCl containing 5% conc. HCl was added dropwise to quench the reaction. The reaction mixture was extracted with ethyl acetate 3x20 ml and the combined organic layers were washed with brine and dried (Na₂SO₄), filtered and concentrated. The crude product was purified by silica gel column chromatography (50% EtOAc/Hex. as eluent) to give 0.12 g of product (75%) (22 mg of starting diol was recovered).

Procedure

To 400 mg (0.93 mmol) of compound 12 dissolved in methanol (10 ml) was added p-TSAH (20 mg), and the solution was stirred at room temperature until TLC showed completion of the reaction (2 hrs). The solvent was removed in vacuo, the residue was dissolved in CH₂Cl₂, washed with sat. NaHCO₃, dried (MgSO₄), and concentrated in vacuo. The crude product was purified by silica gel column chromatography (30% ether in hexanes as eluent) to give 250 mg 13 (78%).

20

Procedure

A suspension of compound (14) (0.12 g, 0.37 mmol), chloroacetonitrile (0.56 g, 7.4 mmol) and K₂CO₃ (0.51 g, 3.7 mmol) in dry acetone (15 ml) was refluxed under Ar for 20 hrs. The reaction mixture was cooled to room temperature and celite (0.5 g) was added. After the mixture was filtered, the solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography using 1:1 EtOAc/hexanes as eluent to yield 0.12 g of product (95%).

Procedure

-n-BuLi (1.1 ml, 1.72 mmol) (1.6 M in hexanes) was added dropwise to a cold (-20°C) and stirred solution of diphenylphosphine (0.28 g, 1.5 mmol) in anhydrous THF (8 ml) under argon. The reaction mixture was warmed to room temperature (20°C). A solution of diol (13) (0.17 g, 0.49 mmol) in dry THF (0.6 ml) was added dropwise to the reaction mixture and the whole solution was heated to reflux for 3 hrs (TLC shows starting material), heating was stopped and the reaction mixture was cooled again to -20°C and diphenylphosphine (0.37 g, 1.96 mmol) was added followed by dropwise addition of n-BuLi (1.5 ml, 2.38 mmol) (1.6 M in hexanes) under argon. After complete addition, the reaction mixture was warmed to 20°C and then refluxed for 18 hrs.

Procedure

Aqueous KOH (0.4 g, 7.12 mmol, water 1.2 ml, 35% solution) was added dropwise to a stirred solution of nitrile compound (15) (0.072 g, 0.21 mmol) in methanol (4 ml) and the reaction mixture was refluxed for 3 hrs. The reaction
mixture was cooled to 10° C., dilute aqueous HCl was added to pH 8 and the solvent was removed in vacuo. Ethyl acetate (20 ml) and aqueous NaCl solution (10 ml) were added and the pH of the reaction mixture was adjusted to between 2 and 3 by addition of 2% HCl. The reaction mixture was extracted with ethyl acetate (2×20 ml). The combined ethyl acetate extracts were washed with brine, dried (Na₂SO₄) and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography using a dichloromethane solution containing 3% methanol and 0.1% acetic acid as eluent to yield 0.076 g of product (95%).

It will be apparent to those skilled in the art that various modifications and variations can be made to the processes and novel intermediates of this invention. Thus, it is intended that the present invention cover such modifications and variations, provided they come within the scope of the appended claims and their equivalents.

The disclosure of all publications cited above are expressly incorporated herein by reference in their entirety to the same extent as if each were incorporated by reference individually.

What is claimed is:

1. A stereoselectively produced isomeric compound according to the following formula:

21

![Chemical Structure](image)

that is produced by a process for making 9-deoxy-PGF₁₄-type compounds, the process comprising cyclizing a starting compound of the formula:

22

![Chemical Structure](image)

wherein R₁ is an alcohol protecting group;

whence R₂ is

(1) —C₄H₉, —CH₃, wherein p is an integer from one to 5, inclusive,

(2) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C₁₋₅)alkyl, or (C₁₋₅)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R₁ is phenoxy or substituted phenoxy, only when R₃ and R₄ are hydrogen or methyl, being the same or different,

(3) phenyl, benzy1, phenethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C₁₋₅) alkyl, or (C₁₋₅)alkoxy, with the proviso that not more than two substituents are other than alkyl,

(4) cis-CH=CH—CH₂—CH₃,

(5) —(CH₂)₁—CH(OH)—CH₃, or

(6) —(CH₂)₂—CH=CH(CH₂)₃;

wherewith Z(C₅H₅)₁—R₂, taken together is

(1) (C₃₋₅)cycloalkyl optionally substituted by one to 3 (C₁₋₅) alkyl;

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

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

(4) 3-thienyloxymethyl;

wherewith M₁ is α-OH;β-R₅ or α-R₅;β-OH or α-R₅;β-R₅ or α-R₅;β-OR₅, wherein R₅ is hydrogen or methyl and R₁ is an alcohol protecting group; and

wherein L₁ is α-R₅;β-R₅ or α-R₅;β-R₅, or a mixture of α-R₅;β-R₅ and α-R₅;β-R₅, 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.

2. The stereoselectively produced isomeric compound of claim 1, wherein Z is O, n is 1, X is COOH, Y₁ is -CH₃, CH₂—M₁ is α-OH;β-R₅, wherein R₅ is hydrogen, L₁ is α-R₅;β-R₅, wherein R₃ and R₄ are hydrogen and R₁ is butyl.

3. A stereoselectively produced isomeric compound according to the following formula:

23

![Chemical Structure](image)

that is produced by a process for making 9-deoxy-PGF₁₄-type compounds, the process comprising cyclizing a starting compound of the formula:

24

![Chemical Structure](image)

by intramolecular cyclization of the enyne,

wherewith

Z is O, S, CH₂, or NR₆ in which R₆ is H, alkyl or aryl;

X is H, CN, OR₆, or COOR₆ in which R₆ is H, alkyl,

a pharmaceutically acceptable cation, THP or TBDMS;

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

wherewith Y₂ is trans-CH=CH—, cis-CH=CH—, CH₂ (CH₂)ₙ—, or —C≡C—; m is 1, 2, or 3;
by intramolecular cyclization of the enyne, wherein
Z is O, S, CH$_2$, or NR$_2$ in which R$_2$ is H, alkyl or aryl;
X is H, CN, OR$_p$, or COOR$_p$ in which R$_p$ is H;
wherein n is 0, 1, 2, or 3;
wherein Y$_1$ is trans-CH$_2$=CH$, \text{cis-CH}$_2$=CH$, -$CH$_2$(CH$_2$r)$_m$-, or =C=C; m is 1,2, or 3;
wherein R$_1$ is an alcohol protecting group;
wherein R$_2$ is
(5) -C$_2$H$_{2p}$-CH$_3$, wherein p is an integer from one to 5, inclusive,
(6) phenoxy optionally substituted by one, two or three chloro, fluoro, trifluoromethyl, (C$_1$-C$_3$)alkyl, or (C$_1$-C$_2$)alkoxy, with the proviso that not more than two substituents are other than alkyl, with the proviso that R$_2$ is phenoxy or substituted phenoxy, only when R$_3$ and R$_4$ are hydrogen or methyl, being the same or different,
(7) phenyl, benzy1, phenylethyl, or phenylpropyl optionally substituted on the aromatic ring by one, two or three chloro, fluoro, trifluoromethyl, (C$_1$-C$_2$) alkyl, or (C$_1$-C$_2$)alkoxy, with the proviso that not more than two substituents are other than alkyl,
(8) cis-CH$_3$=CH$\text{CH}$_2$=CH$_3$,
(9) -(CH$_2$)$_r$-CH(OH)-CH$_3$, or
(10) -(CH$_2$)$_r$-CH=C(CH$_3$)$_2$,
wherein -(C(L$_r$))$_r$-R$_2$ taken together is
(11) (C$_{1r}$-C$_{2r}$)cycloalkyl optionally substituted by one to three (C$_1$-C$_3$) alkyl;
(12) 2-(2-fury1)ethy1,
(13) 2-(3-thieny1)ethy1, or
(14) 3-thieny1oxymethyl;
wherein M$_1$ is oxygen, hydrogen, or methyl, or fluor, and R$_1$ is an alcohol protecting group; and
wherein L$_1$ is a mixture of -R$_3$-$\beta$-R$_4$, where R$_3$ is hydrogen or methyl and R$_4$ is hydrogen, or fluor, being the same or different, with the proviso that one of R$_3$ and R$_4$ is fluor only when the other is hydrogen or fluor.

4. A stereoselectively produced isomeric compound in pharmacologically acceptable salt form according to the following formula:

that is produced by process for making 9-deoxy-PGF$_1^+$ type compounds, the process comprising cyclizing a

* * * * *