

[54] COMPOSITION AND PROCESS

[75] Inventor: Paul A. Aristoff, Portage, Mich.

[73] Assignee: The Upjohn Company, Kalamazoo, Mich.

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[56] References Cited

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Primary Examiner—Paul J. Killos
Attorney, Agent, or Firm—L. Ruth Hattan; Robert A. Armitage

[57] ABSTRACT

The present specification provides novel analogs of carbacyclin (CBA₂), 6a-carba-prostacyclin (6a-carba-PGI₂), which have pronounced prostacyclin-like pharmacological activity, e.g., as platelet antiaggregatory agents. Specifically the novel chemical analogs of CBA₂ are those substituted by fluoro (C-5), alkyl (C-9), interphenylene (C-5), and methano (C-6a,9). Further provided are benzindene analogs of CBA₂ and substituted forms thereof, i.e., 9-deoxy-2',9-methano (or 2',9-metheno)-3-oxa-4,5,6-trinor-3,7-(1',3'-interphenylene)-PGF₁ compounds. Also provided are a variety of novel chemical intermediates, e.g., substituted bicyclo[3.3.0]octane intermediates, and chemical process utilizing such intermediates which are useful in the preparation of the novel CBA₂ analogs.

13 Claims, No Drawings

COMPOSITION AND PROCESS

This application is a continuation-in-part of Ser. No. 135,055, filed Mar. 28, 1980, now abandoned.

BACKGROUND OF THE INVENTION

The present invention relates to novel compositions of matter and novel processes for preparing these compositions of matter. Moreover, there are provided novel methods by which certain of these novel compositions of matter are employed for pharmacologically useful purposes. Further there are provided novel chemical intermediates for preparing these compositions of matter.

The present invention is specifically concerned with novel analogs of prostacyclin or PGI₂. Specifically, the present invention is concerned with analogs of carbacyclin modified at the C-5 or C-9 position, e.g., C-5 interphenylene analogs of carbacyclin, 5-fluoro analogs of carbacyclin, 9 β -alkyl analogs of carbacyclin, C-6a,9 tricyclic (cyclopropyl) analogs of carbacyclin, and combinations thereof as well as novel benzidene analogs thereof.

Prostacyclin is an endogenously produced compound in mammalian species, being structurally and biosynthetically related to the prostaglandins (PG's). In particular, prostacyclin exhibits the structure and carbon atom numbering of formula I when the C-5,6 positions are unsaturated. For convenience, prostacyclin is often referred to simply as "PGI₂". Carbacyclin, 6a-carba-PGI₂, exhibits the structure and carbon atom numbering indicated in formula II when the C-5,6 positions are unsaturated. Likewise, for convenience, carbacyclin is referred to simply as "CBA₂".

A stable partially saturated derivative of PGI₂ is PGI₁ or 5,6-dihydro-PGI₂ when the C-5,6 positions are saturated, depicted with carbon atom numbering in formula II when the C-5,6 positions are saturated. The corresponding 5,6-dihydro-CBA₂ is CBA₁, depicted in formula II.

As is apparent from inspection of formulas I and II, prostacyclin and carbacyclin may be trivially named as derivatives of PGF-type compounds, e.g., PGF₂ α of formula III. Accordingly, prostacyclin is trivially named 9-deoxy-6,9 α -epoxy-(5Z)-5,6-didehydro-PGF₁ and carbacyclin is named 9-deoxy-6,9 α -methano-(5E)-5,6-didehydro-PGF₁. For description of prostacyclin and its structural identification, see Johnson, et al., Prostaglandins 12:915 (1976).

For convenience, the novel prostacyclin or carbacyclin analogs 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, PGI₂ derivatives, or preferably as CBA₁ or CBA₂ derivatives.

In the formulas herein, broken line attachments to a ring indicate substituents in the "alpha" (α) configuration, i.e., below the plane of said ring. Heavy solid line attachments to a ring indicate substituents in the "beta" (β) configuration, i.e., above the plane of said ring. The use of wavy lines (~) herein will represent attachment of substituents in the alpha or beta configuration or attached in a mixture of alpha and beta configurations. Alternatively wavy lines will represent either an E or Z

geometric isomeric configuration or the mixture thereof.

A side chain hydroxy at C-15 in the formulas herein is in the S or R configuration as determined by the Cahn-Ingold-Prelog sequence rules, J. Chem. Ed. 41:16 (1964). See also Nature 212:38 (1966) for discussion of the stereochemistry of the prostaglandins which discussion applies to the novel prostacyclin or carbacyclin analogs herein. Molecules of prostacyclin and carbacyclin each have several centers of asymmetry and therefore can exist in optically inactive form or in either of two enantiomeric (optically active) forms, i.e., the dextrorotatory and laevorotatory forms. As drawn, the formula for PGI₂ corresponds to that endogenously produced in the mammalian species. In particular, refer to the stereochemical configuration at C-8 (α), C-9 (α), C-11 (α) and C-12 (β) of endogenously produced prostacyclin. The mirror image of the above formula for prostacyclin represents the other enantiomer. The racemic form of prostacyclin contains equal numbers of both enantiomeric molecules.

For convenience, reference to prostacyclin and carbacyclin will refer to the optically active form thereof. Thus, with reference to prostacyclin, reference is made to the form thereof with the same absolute configuration as that obtained from the mammalian species.

The term "prostacyclin-type" product, as used herein, refers to any cyclopentane derivative herein which is useful for at least one of the same pharmacological purposes for which prostacyclin is employed. A formula as drawn herein which depicts a prostacyclin-type product or an intermediate useful in the preparation thereof, represents that particular stereoisomer of the prostacyclin-type product which is of the same relative stereochemical configuration as prostacyclin obtained from mammalian tissues or the particular stereoisomer of the intermediate which is useful in preparing the above stereoisomer of the prostacyclin type product.

The term "prostacyclin analog" or "carbacyclin analog" represents that stereoisomer of a prostacyclin-type product which is of the same relative stereochemical configuration as prostacyclin obtained from mammalian tissues or a mixture comprising stereoisomer and the enantiomers thereof. In particular, where a formula is used to depict a prostacyclin type product herein, the term "prostacyclin analog" or "carbacyclin analog" refers to the compound of that formula or a mixture comprising that compound and the enantiomer thereof.

PRIOR ART

Carbacyclin and closely related compounds are known in the art. See Japanese Kokia 63,059 and 63,060, also abstracted respectively as Derwent Farmdoc CPI Numbers 48154B/26 and 48155B/26. See also British published specifications 2,012,265 and German Offenlegungsschrift 2,900,352, abstracted as Derwent Farmdoc CPI Number 54825B/30. See also British published application Nos. 2,017,699, 2,014,143 and 2,013,661.

The synthesis of carbacyclin and related compounds is also reported in the chemical literature, as follows: Morton, D. R., et al., J. Organic Chemistry, 44:2880 (1979); Shibasaki, M., et al. Tetrahedron Letters, 433-436 (1979); Kojima, K., et al., Tetrahedron Letters, 3743-3746 (1978); Nicolaou, K. C., et al., J. Chem. Soc., Chemical Communications, 1067-1068 (1978); Sugie, A., et al., Tetrahedron Letters 2607-2610 (1979); Shibasaki, M., Chemistry Letters, 1299-1300 (1979),

and Hayashi, M., Chem. Lett. 1437-1440 (1979); and Li, Tsung-tee, "A Facile Synthesis of 9(0)-Methano-prosta-cyclin", Abstract No. 378, (Organic Chemistry), and P. A. Aristoff, "Synthesis of 6a-Carbaprostacyclin I₂", Abstract No. 236 (Organic Chemistry) both at Abstract of Papers (Part II) Second Congress of the North American Continent, San Francisco, California (Las Vegas, Nevada), USA, 24-29 August 1980.

7-Oxo and 7-hydroxy-CBA₂ compounds are appar-
ently disclosed in U.S. Pat. No. 4,192,891. 19-Hydroxy-
CBA₂ compounds are disclosed in U.S. Ser. No. 54,811,
filed 5 July 1979. CBA₂ aromatic esters are disclosed in
U.S. Pat. No. 4,180,657. 11-Deoxy-Δ¹⁰- or Δ¹¹-CBA₂
compounds are described in Japanese Kokai No.
77/24,865, published 24 Feb. 1979.

SUMMARY OF THE INVENTION

The present specification particular by provides:

- (a) a carbacyclin intermediate of formula IV, V, VI,
VII, VIII, or IX; and
(b) a carbacyclin analog of formula X or XI;
wherein g is 0, 1, 2, or 3;
wherein n is one or 2;
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 hy-
drogen, 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 M₆ is α-OR₁₀:β-R₅ or α-R₅:β-OR₁₀, wherein
R₅ is hydrogen or methyl and R₁₀ is an acid hydrolyz-
able protective group;
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 (C₁-C₃)alkoxy, with the proviso
that not more than two substituents are other than
alkyl,
(4) cis—CH=CH—CH₂—CH₃,
(5) —(CH₂)₂—CH(OH)—CH₃, or
(6) —(CH₂)₃—CH=C(CH₃)₂;
wherein —C(L₁)-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 R₁₅ is hydrogen or fluoro;
wherein R₁₆ is hydrogen or R₁₆ and R₁₇ taken to-
gether are —CH₂— or R₁₆ and R₁₇ taken together form
a second valence bond between C-6a and C-9 or are
—CH₂—;
wherein R₁₇ is as defined above or is
(1) hydrogen, or
(2) (C₁-C₄)alkyl;

wherein R₁₈ is hydrogen, hydroxy, hydroxymethyl,
—OR₁₀ or —CH₂OR₁₀, wherein R₁₀ is an acid-hydro-
lyzable protective group; 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 and R₂₄ 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 R₂₇ is the same as R₇ except that —(CH₂-
)₂—CH(OH)—CH₃ is —(CH₂)—CH(OR₁₁)—CH₃;

wherein R₃₂ is hydrogen or R₃₁, wherein R₃₁ is a
hydroxyl hydrogen replacing group;

wherein R₃₃ is —CHO or —CH₂OR₃₂, wherein R₃₂ is
as defined above;

wherein R₄₇ is as defined above or is

(1) (C₁-C₄)alkyl, or

(2) —CH₂OH;

wherein X₁ is

(1) —COOR₁, wherein R₁ is

(a) hydrogen,

(b) (C₁-C₁₂)alkyl,

(c) (C₃-C₁₀)cycloalkyl,

(d) (C₇-C₁₂)aralkyl,

(e) phenyl, optionally substituted with one, 2 or 3
chloro or (C₁-C₃)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, ben-
zamidophenyl, 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)alkoxycarbo-
nyl, 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 (C₁-C₃)alkyl,

(xiii) (C₁-C₄)hydroxyalkyl,

(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 pyrrolidino, piperidino, morpholino, piperazino, hexamethylenimine, 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 R₂₃ is hydrogen or (C₁-C₄)alkyl and R₅₁ is other than hydrogen, but otherwise as defined above,

(d) sulfonylamino of the formula —NR₅₃SO₂R₅₁, wherein R₂₁ and R₂₃ 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—;

wherein Z₁ is

(1) —CH₂—(CH₂)_f—C(R₂)₂, wherein R₂ is hydrogen or fluoro and f is zero, one, 2, or 3;

(2) trans—CH₂—CH=CH—,

(3) —(Ph)—(CH₂)_g—, wherein (Ph) is 1,2-, 1,3-, or 1,4-phenylene and g is zero, one, 2, or 3;

wherein Z₄ is —CH₂— or —(CH₂)_f—CF₂, wherein f is as defined above;

with the overall proviso that

(1) R₁₅, R₁₆, and R₁₇ are all hydrogen only when Z₁ is —(Ph)—(CH₂)_g—, and

(2) Z₁ is —(Ph)—(CH₂)_g— only when R₁₅ is hydrogen.

With regard to the divalent substituents described above (e.g., L₁ and M₁), these divalent radicals are defined as α-R_i:β-R_j, wherein R_i represents the substituent of the divalent moiety in the alpha configuration with respect to the plane of the C-8 to C-12 cyclopentane ring and R_j represents the substituent of the divalent moiety in the beta configuration with respect to the plane of the ring. Accordingly, when M₁ is defined as α-OH:β-R₅, the hydroxy of the M₁ moiety is in the alpha configuration, i.e., as in PGI₂ above, and the R₅ substituent is in the beta configuration.

The carbon atom content of various hydrocarbon-containing moieties is indicated by a prefix designating the minimum and maximum number of carbon atoms in the moiety, i.e., the prefix (C_i-C_j) indicates a moiety of the integer "i" to the integer "j" carbon atoms, inclusive. Thus (C₁-C₃)alkyl refers to alkyl of one to 3 carbon atoms, inclusive, or methyl, ethyl, propyl, and isopropyl.

Certain novel prostacyclin analogs herein, i.e., formula X compounds, are all named as CBA₁ or CBA₂ compounds, respectively, by virtue of the substitution of methylene for oxa in the heterocyclic ring of prostacyclin and the substitution. CBA₂ compounds are those exhibiting the olefinic double bond at C-5,6, while CBA₁ compounds are those saturated at C-5,6. Formula XI compounds are named as PGE₁ or PGF₁ derivatives as hereinafter described.

Novel compounds wherein Z₁ is (Ph)-(CH₂)_g are designated inter-o-, inter-m-, or inter-p-phenylene depending on whether the attachment between C-5 and the —(CH₂)_g— moiety is ortho, meta, or para, respectively.

For those compounds wherein g is zero, one, 2 or 3, the carbacyclin analogs so described are further characterized as 2,3,4-trinor-, 3,4-dinor-, or 4-nor, since in this event the X₁-terminated side chain contains (not including the phenylene) 2, 3, or 4 carbon atoms, respectively, in place of the five carbon atoms contained in PGI₂. The missing carbon atom or atoms are considered to be at the C-4 to C-2 positions such that the phenylene is connected to the C-5 and C-1 to C-3 positions. Accordingly these compounds are named as 1,5-, 2,5-, 3,5-, and 4,5-inter-phenylene CBA compounds when g is zero, one, 2, or 3, respectively.

Those CBA analogs wherein Z₁ is —CH₂—(CH₂)_f—CF₂— are characterized as "2,2-difluoro—" compounds. For those compounds wherein f is zero, 2, or 3, the carbacyclin analogs so described are further characterized as 2-nor, 2a-homo, or 2a,2b-dihomo, since in this event the X₁-terminated side chain contains 4, 6, or 7 carbon atoms, respectively, in place of the five carbon atoms contained in CBA₂. The missing carbon atom is considered to be at the C-2 position such that the C-1 carbon atoms is connected to the C-3 position. The additional carbon atom or atoms are considered as though they were inserted between the C-2 and C-3 positions. Accordingly these additional carbon atoms are referred to as C-2a and C-2b, counting from the C-2 to the C-3 position.

Those CBA analogs wherein Z₁ is trans—CH₂—CH=CH— are described as "trans-2,3-didehydro-CBA" compounds.

Those novel compounds where n is 2 are further characterized as 7a-homo-CBA compounds by virtue of the cyclohexyl ring replacing the heterocyclic ring of prostacyclin.

Further, the novel compounds are named as 9β-alkyl-CBA compounds when R₁₇ is alkyl.

When R₁₆ and R₁₇ taken together are —CH₂—(methylene), the novel compounds so described are "6α,9β-methano-CBA" compounds by virtue of the methylene bridge between C-6a and C-9.

When R₁₅ is fluoro, "5-fluoro-CBA" compounds are described.

The formula XI CBA analogs wherein R₂₀, R₂₁, R₂₂, R₂₃, and R₂₄ are all hydrogen with R₂₂ being β-hydrogen are characterized as "9-deoxy-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-inter-phenylene)-PGF₁" compounds. Corresponding compounds wherein R₂₂ is α-hydrogen are characterized as "9-deoxy-2',9β-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-inter-phenylene)-PGF₁" compounds. CBA analogs wherein R₂₀, R₂₃, and R₂₄ are all hydrogen and R₂₁ and R₂₂ taken together form a valence bond between C-9 and C-6a are characterized as "9-deoxy-2',9-metheno-3-oxo-3,4,5-trinor-3,7-(1',3'-inter-phenylene)-PGF₁" compounds. CBA analogs wherein R₂₀ is hydrogen and R₂₁ and R₂₂ taken together form a second valence bond between C-9 and C-6a and R₂₃ and R₂₄ taken together form a second valence bond between C-7 and C-8 are characterized as "9-deoxy-2',9-metheno-3-oxa-3,4,5-trinor-3,7-(1',3'-inter-phenylene)-7,8-didehydro-PGE₁" compounds. The formula XI CBA analogs wherein R₂₂, R₂₃, and R₂₄ are all hydrogen and R₂₀ and R₂₁ taken together are oxo are characterized as "6a-oxo-9-deoxy-2',9α-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-inter-phenylene)-PGF₁" or "6a-oxo-9-deoxy-2',9β-methano-3-oxa-4,5,6-trinor-3,7-(1',3'-inter-phenylene)-PGF₁" depending on whether R₂₂ is α-hydrogen or β-hydrogen, respectively. Formula XI CBA analogs wherein R₂₀, R₂₂, R₂₃, and R₂₄

are all hydrogen and R₂₁ is α -hydroxy are characterized as "6 α -hydroxy-9-deoxy-2',9 α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-inter-phenylene)-PGF₁" or "6 α -hydroxy-9-deoxy-2',9 β -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-inter-phenylene)-PGF₁" compounds depending on whether R₂₂ is α -hydrogen or β -hydrogen, respectively. Finally, formula XI TXA analogs wherein R₂₀, R₂₂, R₂₃, and R₂₄ are all hydrogen and R₂₁ is β -hydroxy are characterized as "6 $\alpha\beta$ -hydroxy-9-deoxy-2',9 β -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-inter-phenylene)-PGF₁" or "6 $\alpha\beta$ -hydroxy-9-deoxy-2',9 α -methano-3-oxa-4,5,6-trinor-3,7-(1',3'-inter-phenylene)-PGF₁" compounds depending on whether R₂₂ is α -hydrogen or β -hydrogen, respectively. When Z₄ is $-(CH_2)_f-CF_2$ and f is zero, the formula XI CBA analogs are additionally characterized as "2,2-difluoro" compounds. When f is one, 2, or 3, such compounds are additionally characterized as "2a-homo", "2a,2b-dihomo" or "2a,2b,2c-trihomo" compounds.

When R₅ is methyl, the carbacyclin analogs are all named as "15-methyl-CBA" compounds. Further, except for compounds wherein Y₁ is $cis-CH=CH-$, compounds wherein the M₁ moiety contains an hydroxyl in the beta configuration are additionally named as "15-epi-CBA" compounds.

For the compounds wherein Y₁ is $cis-CH=CH-$, then compounds wherein the M₁ moiety contains an hydroxyl in the alpha configuration are named as "15-epi-CBA" compounds. For a description of this convention of nomenclature for identifying C-15 epimers, see U.S. Pat. No. 4,016,184, issued 5 Apr. 1977, particularly columns 24-27 thereof.

The novel carbacyclin analogs herein which contain $-(CH_2)_2-$, $cis-CH=CH-$, or $-C\equiv C-$ as the Y₁ moiety, are accordingly referred to as "13,14-dihydro", "cis-13", or "13,14-didehydro" compounds, respectively.

When R₇ is straight chained $-C_mH_{2m}-CH_3$, wherein m is as defined above, the compounds so described are named as "19,20-dinor", "20-nor", "20-methyl" or "20-ethyl" compounds when m is one, 2, 4 or 5, respectively. When R₇ is branched chain $-C_mH_{2m}-CH_3$, then the compounds so described are "17-, 18-, 19-, or 20-alkyl" or "17,17-, 17,18-, -17,19-, 17,20-, 18,18-, 18,19-, 18,20-, 19,19-, or 19,20-dialkyl" compounds when m is 4 or 5 and the unbranched portion of the chain is at least n-butyl, e.g., "17,20-dimethyl" compounds are described when m is 5 (1-methylpentyl).

When R₇ is phenyl and neither R₃ and R₄ is methyl, the compounds so described are named as "16-phenyl-17,18,19,20-tetranor" compounds. When R₇ is substituted phenyl, the corresponding compounds are named as "16-(substituted phenyl)-17,18,19,20-tetranor" compounds. When one and only one of R₃ and R₄ is methyl or both R₃ and R₄ are methyl, then the corresponding compounds wherein R₇ is as defined in this paragraph are named as "16-phenyl or 16-(substituted phenyl)-18,19,20-trinor" compounds or "16-methyl-16-phenyl- or 16-(substituted phenyl)-18,19,20-trinor" compounds respectively.

When R₇ is benzyl, the compounds so described are named as "17-phenyl-18,19,20-trinor" compounds. When R₇ is substituted benzyl, the corresponding compounds are named as "17-(substituted phenyl)-18,19,20-trinor" compounds.

When R₇ is phenylethyl, the compounds so described are named as "18-phenyl-19,20-dinor" compounds. When R₇ is substituted phenylethyl, the corresponding

compounds are named as "18-(substituted phenyl)-19,20-dinor" compounds.

When R₇ is phenylpropyl, the compounds so described are named as "19-phenyl-20-nor" compounds. When R₇ is substituted phenylpropyl the corresponding compounds are named as "19-(substituted phenyl)-20-nor" compounds.

When R₇ is phenoxy and neither R₃ nor R₄ is methyl, the compounds so described are named as "16-phenoxy-17,18,19,20-tetranor" compounds. When R₇ is substituted phenoxy, the corresponding compounds are named as "16-(substituted phenoxy)-17,18,19,20-tetranor" compounds. When one and only one of R₃ and R₄ is methyl or both R₃ and R₄ are methyl, then the corresponding compounds wherein R₇ is as defined in this paragraph are named as "16-phenoxy or 16-(substituted phenoxy)-18,19,20-trinor" compounds or "16-methyl-16-phenoxy- or 16-(substituted phenoxy)-18,19,20-trinor" compounds, respectively.

When R₇ is $cis-CH=CH-CH_2CH_3$, the compounds so described are named as "cis-17,18-didehydro" compounds.

When R₇ is $-(CH_2)_2-CH(OH)-CH_3$, the compounds so described are named as "19-hydroxy" compounds.

When R₇ is $-(CH_2)_3-CH=C(CH_3)_2$, the compounds so described are named as "20-isopropylidene" compounds.

When $-C(L_1)-R_7$ is optionally substituted cycloalkyl, 2-(2-furyl)ethyl, 2-(3-thienyl)ethyl, or 3-thienyloxymethyl, the compounds so described are respectively 15-cycloalkyl-16,17,18,19,20-pentanor compounds, 17-(2-furyl)-18,19,20-trinor-CBA compounds, 17-(3-thienyl)-18,19,20-trinor compounds, or 16-(3-thienyloxy)-17,18,19,20-tetranor compounds.

When at least one of R₃ and R₄ is not hydrogen then (except for the 16-phenoxy or 16-phenyl compounds discussed above) there are described the "16-methyl" (one and only one of R₃ and R₄ is methyl), "16,16-dimethyl" (R₃ and R₄ are both methyl), "16-fluoro" (R₃ or R₄ is fluoro), "16,16-difluoro" (R₃ and R₄ are both fluoro) compounds. For those compounds wherein R₃ and R₄ are different, the prostaglandin analogs so represented contain an asymmetric carbon atom at C-16. Accordingly, two epimeric configurations are possible: "(16S)" and "(16R)". Further, there is described by this invention the C-16 epimeric mixture: "(16RS)".

When X₁ is $-CH_2OH$, the compounds so described are named as "2-decarboxy-2-hydroxymethyl" compounds.

When X₁ is $-CH_2NL_2L_3$, the compounds so described are named as "2-decarboxy-2-aminomethyl" or "2-(substituted amino)methyl" compounds.

When X₁ is $-COL_4$, the novel compounds herein are named as CBA-type amides. Further, when X₁ is $-COOR_1$, the novel compounds herein are named as CBA-type esters and CBA-type salts.

Examples of phenyl esters substituted in the para position (i.e., X₁ is $-COOR_1$, R₁ is p-substituted phenyl) include p-acetamidophenyl ester, p-benzamidophenyl ester, p-(p-acetamidobenzamido)phenyl ester, p-(p-benzamidobenzamido)phenyl ester, p-aminocarbonylaminophenyl ester, p-acetylphenyl ester, p-benzylphenyl ester, p-amidocarbonylphenyl ester, p-methoxycarbonylphenyl ester, p-benzoyloxyphenyl ester, p-(p-acetamidobenzoyloxy)phenyl ester, and p-hydroxybenzaldehyde semicarbazone ester.

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