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Aristoff

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[54] **COMPOSITION AND PROCESS**

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[56] **References Cited**

FOREIGN PATENT DOCUMENTS

2017699 10/1979 United Kingdom 810/56

OTHER PUBLICATIONS

Derwent Abstract 48154B/26 J 54063059 05/21/79.

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[57] **ABSTRACT**

The present specification provides novel analogs of carbacyclin (CBA_2), 6a-carba-prostacyclin (6a-carba-PGI_2), which have pronounced prostacyclin-like pharmacological activity, e.g., as platelet antiaggregatory agents. Specifically the novel chemical analogs of CBA_2 are those substituted by fluoro (C-5), alkyl (C-9), interphenylene (C-5), and methano (C-6a,9). Further provided are benzindene analogs of CBA_2 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)-PGF_1compounds. 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 CBA_2 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 PGI_2. 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, 9β-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 "PGI_2". Carbacyclin, 6a-carba-PGI_2, 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 "CBA_2".

A stable partially saturated derivative of PGI_2 is PGI_1 or 5,6-dihydro-PGI_2 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-CBA_2 is CBA_1, 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., $PGF_2\alpha$ of formula III. Accordingly, prostacyclin is trivially named 9-deoxy-6,9α-epoxy-(5Z)-5,6-didehydro-PGF_1 and carbacyclin is named 9-deoxy-6,9α-methano-(5E)-5,6-didehydro-PGF_1. 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-PGF_1-type compounds, PGI_2 derivatives, or preferably as CBA_1 or CBA_2 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 ($\sim$) 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 laveorotatory forms. As drawn, the formula for PGI_2 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 Offenlungsschrift 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-prostacyclin", Abstract No. 378, (Organic Chemistry), and P. A. Aristoff, "Synthesis of 6a-Carbaprostacyclin I_2", 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-CBA_2 compounds are apparently disclosed in U.S. Pat. No. 4,192,891. 19-Hydroxy-CBA_2 compounds are disclosed in U.S. Ser. No. 54,811, filed 5 July 1979. CBA_2 aromatic esters are disclosed in U.S. Pat. No. 4,180,657. 11-Deoxy-Δ^{10}- or Δ^{11}-CBA_2 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 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 M_6 is α-OR_{10}:β-R_5 or α-R_5:β-OR_{10}, wherein R_5 is hydrogen or methyl and R_{10} is an acid hydrolyzable protective group;

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 (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 R_8 is hydroxy, hydroxymethyl, or hydrogen;

wherein R_{15} is hydrogen or fluoro;

wherein R_{16} is hydrogen or R_{16} and R_{17} taken together are —CH_2— or R_{16} and R_{47} taken together form a second valence bond between C-6a and C-9 or are —CH_2—;

wherein R_{17} is as defined above or is

(1) hydrogen, or

(2) (C_1-C_4)alkyl;

wherein R_{18} is hydrogen, hydroxy, hydroxymethyl, —OR_{10} or —CH_2OR_{10}, wherein R_{10} is an acid-hydrolyzable protective group; 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-6a, and R_{23} and R_{24} taken together form a second valence bond between C-8 and C-9 or are both hydrogen, 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 hydrogen and R_{21} is hydroxy, being α-hydroxy or β-hydroxy;

wherein R_{27} is the same as R_7 except that —$(CH_2)_2$—CH(OH)—CH_3 is —(CH_2)—$CH(OR_{11})$—CH_3;

wherein R_{32} is hydrogen or R_{31}, wherein R_{31} is a hydroxyl hydrogen replacing group;

wherein R_{33} is —CHO or —CH_2OR_{32}, wherein R_{32} is as defined above;

wherein R_{47} is as defined above or is

(1) (C_1-C_4)alkyl, or

(2) —CH_2OH;

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_7-C_{12})aralkyl,

(e) phenyl, optionally substituted with one, 2 or 3 chloro or (C_1-C_3)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 acceptable 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 one, 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 (C_1-C_3)alkyl,

(xiii) (C_1-C_4)hydroxyalkyl,

(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 pyrolidino, 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_{23} 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_{21} and R_{23} are as defined in (c),

(4) $—CH_2NL_2L_3$, wherein L_2 and L_3 are hydrogen 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—;

wherein Z_1 is

(1) $—CH_2—(CH_2)_f—C(R_2)_2$, wherein R_2 is hydrogen or fluoro and f is zero, one, 2, or 3;

(2) trans—CH_2—CH=CH—,

(3) —(Ph)—$(CH_2)_g$—, wherein (Ph) is 1,2-, 1,3-, or 1,4-phenylene and g is zero, one, 2, or 3;

wherein Z_4 is $—CH_2—$ or $—(CH_2)_f—CF_2$, wherein f is as defined above;

with the overall proviso that

(1) R_{15}, R_{16}, and R_{17} are all hydrogen only when Z_1 is —(Ph)—$(CH_2)_g$—, and

(2) Z_1 is —(Ph)—$(CH_2)_g$— only when R_{15} is hydrogen.

With regard to the divalent substituents described above (e.g., L_1 and M_1), 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 M_1 is defined as α-OH;β-R_5, the hydroxy of the M_1 moiety is in the alpha configuration, i.e., as in PGI_2 above, and the R_5 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 (C_1–C_3)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 CBA_1 or CBA_2 compounds, respectively, by virtue of the substitution of methylene for oxa in the heterocyclic ring of prostacyclin and the substitution. CBA_2 compounds are those exhibiting the olefinic double bond at C-5,6, while CBA_1 compounds are those saturated at C-5,6. Formula XI compounds are named as PGE_1 or PGF_1 derivatives as hereinafter described.

Novel compounds wherein Z_1 is (Ph)-$(CH_2)_g$ are designated inter-o-, inter-m-, or inter-p-phenylene depending on whether the attachment between C-5 and the $—(CH_2)_g—$ 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 X_1-terminated side chain contains (not including the phenylene) 2, 3, or 4 carbon atoms, respectively, in place of the five carbon atoms contained in PGI_2. 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 Z_1 is $—CH_2—(CH_2)_f—CF_2—$ 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 X_1-terminated side chain contains 4, 6, or 7 carbon atoms, respectively, in place of the five carbon atoms contained in CBA_2. 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 Z_1 is trans—CH_2—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 R_{17} is alkyl.

When R_{16} and R_{17} taken together are $—CH_2—$(-methylene), the novel compounds so described are "6$\alpha\beta$,9β-methano-CBA" compounds by virtue of the methylene bridge between C-6a and C-9.

When R_{15} is fluoro, "5-fluoro-CBA" compounds are described.

The formula XI CBA analogs wherein R_{20}, R_{21}, R_{22}, R_{23}, and R_{24} are all hydrogen with R_{22} being β-hydrogen are characterized as "9-deoxy-2′,9α-methano-3-oxa-4,5,6-trinor-3,7-(1′,3′-inter-phenylene)-PGF_1" compounds. Corresponding compounds wherein R_{22} is α-hydrogen are characterized as "9-deoxy-2′,9β-methano-3-oxa-4,5,6-trinor-3,7-(1′,3′-inter-phenylene)-PGF_1" compounds. CBA analogs wherein R_{20}, R_{23}, and R_{24} are all hydrogen and R_{21} and R_{22} taken together form a valence bond between C-9 and C-6a are characterized as "9-deoxo-2′,9-metheno-3-oxo-3,4,5-trinor-3,7-(1′,3′-inter-phenylene)-PGF_1" compounds. CBA analogs wherein R_{20} is hydrogen and R_{21} and R_{22} taken together form a second valence bond between C-9 and C-6a and R_{23} and R_{24} taken together form a second valence bond between C-7 and C-8 are characterized as "9-deoxo-2′,9-metheno-3-oxa-3,4,5-trinor-3,7-(1′,3′-inter-phenylene)-7,8-didehydro-PGE_1" compounds. The formula XI CBA analogs wherein R_{22}, R_{23}, and R_{24} are all hydrogen and R_{20} and R_{21} 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)-PGF_1" or "6a-oxo-9-deoxy-2′,9β-methano-3-oxa-4,5,6-trinor-3,7-(1′,3′-inter-phenylene)-PGF_1" depending on whether R_{22} is α-hydrogen or β-hydrogen, respectively. Formula XI CBA analogs wherein R_{20}, R_{22}, R_{23}, and R_{24}

are all hydrogen and R_{21} is α-hydroxy are characterized as "6aα-hydroxy-9-deoxy-2′,9α-methano-3-oxa-4,5,6-trinor-3,7-(1′,3′-inter-phenylene)-PGF_1" or "6aα-hydroxy-9-deoxy-2′,9β-methano-3-oxa-4,5,6-trinor-3,7-(1′,3′-inter-phenylene)-PGF_1" compounds depending on whether R_{22} is α-hydrogen or β-hydrogen, respectively. Finally, formula XI TXA analogs wherein R_{20}, R_{22}, R_{23}, and R_{24} are all hydrogen and R_{21} is β-hydroxy are characterized as "6aβ-hydroxy-9-deoxy-2′,9β-methano-3-oxa-4,5,6-trinor-3,7-(1′,3′-inter-phenylene)-PGF_1" or "6aβ-hydroxy-9-deoxy-2′,9α-methano-3-oxa-4,5,6-trinor-3,7-(1′,3′-inter-phenylene)-PGF_1" compounds depending on whether R_{22} is α-hydrogen or β-hydrogen, respectively. When Z_4 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 R_5 is methyl, the carbacyclin analogs are all named as "15-methyl-CBA" compounds. Further, except for compounds wherein Y_1 is cis—CH=CH—, compounds wherein the M_1 moiety contains an hydroxyl in the beta configuration are additionally named as "15-epi-CBA" compounds.

For the compounds wherein Y_1 is cis—CH=CH—, then compounds wherein the M_1 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≡C— as the Y_1 moiety, are accordingly referred to as "13,14-dihydro", "cis-13", or "13,14-didehydro" compounds, respectively.

When R_7 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 R_7 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 R_7 is phenyl and neither R_3 and R_4 is methyl, the compounds so described are named as "16-phenyl-17,18,19,20-tetranor" compounds. When R_7 is substituted phenyl, the corresponding compounds are named as "16-(substituted phenyl)-17,18,19,20-tetranor" compounds. When one and only one of R_3 and R_4 is methyl or both R_3 and R_4 are methyl, then the corresponding compounds wherein R_7 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 R_7 is benzyl, the compounds so described are named as "17-phenyl-18,19,20-trinor" compounds. When R_7 is substituted benzyl, the corresponding compounds are named as "17-(substituted phenyl)-18,19,20-trinor" compounds.

When R_7 is phenylethyl, the compounds so described are named as "18-phenyl-19,20-dinor" compounds. When R_7 is substituted phenylethyl, the corresponding compounds are named as "18-(substituted phenyl)-19,20-dinor" compounds.

When R_7 is phenylpropyl, the compounds so described are named as "19-phenyl-20-nor" compounds. When R_7 is substituted phenylpropyl the corresponding compounds are named as "19-(substituted phenyl)-20-nor" compounds.

When R_7 is phenoxy and neither R_3 nor R_4 is methyl, the compounds so described are named as "16-phenoxy-17,18,19,20-tetranor" compounds. When R_7 is substituted phenoxy, the corresponding compounds are named as "16-(substituted phenoxy)-17,18,19,20-tetranor" compounds. When one and only one of R_3 and R_4 is methyl or both R_3 and R_4 are methyl, then the corresponding compounds wherein R_7 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 R_7 is cis—CH=CH—CH_2CH_3, the compounds so described are named as "cis-17,18-didehydro" compounds.

When R_7 is $—(CH_2)_2—CH(OH)—CH_3$, the compounds so described are named as "19-hydroxy" compounds.

When R_7 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-thienyl-)oxy-17,18,19,20-tetranor compounds.

When at least one of R_3 and R_4 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 R_3 and R_4 is methyl), "16,16-dimethyl" (R_3 and R_4 are both methyl), "16-fluoro" (R_3 or R_4 is fluoro), "16,16-difluoro" (R_3 and R_4 are both fluoro) compounds. For those compounds wherein R_3 and R_4 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 X_1 is $—CH_2OH$, the compounds so described are named as "2-decarboxy-2-hydroxymethyl" compounds.

When X_1 is $—CH_2NL_2L_3$, the compounds so described are named as "2-decarboxy-2-aminomethyl" or "2-(substituted amino)methyl" compounds.

When X_1 is $—COL_4$, the novel compounds herein are named as CBA-type amides. Further, when X_1 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., X_1 is $—COOR_1$, R_1 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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