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**Aristoff**

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[54] **COMPOSITION AND PROCESS**


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[63] Continuation-in-part of Ser. No. 135,055, Mar. 28, 1980, abandoned.

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[56] **References Cited**

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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)-$PGF_1$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 $CBA_2$ 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, 9$\beta$-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-6,9$\alpha$-epoxy-(5Z)-5,6-didehydro-$PGF_1$ and carbacyclin is named 9-deoxy-6,9$\alpha$-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" ($\alpha$) configuration, i.e., below the plane of said ring. Heavy solid line attachments to a ring indicate substituents in the "beta" ($\beta$) 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 ($\alpha$), C-9 ($\alpha$), C-11 ($\alpha$) and C-12 ($\beta$) 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-$\Delta^{10}$- or $\Delta^{11}$-$CBA_2$ 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 $\alpha$-$R_3$:$\beta$-$R_4$, $\alpha$-$R_4$:$\beta$-$R_3$, 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;

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

wherein $M_6$ is $\alpha$-$OR_{10}$:$\beta$-$R_5$ or $\alpha$-$R_5$:$\beta$-$OR_{10}$, 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 $\alpha$-hydrogen or $\beta$-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 $\alpha$-hydrogen or $\beta$-hydrogen, and

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

(b) $R_{20}$ is hydrogen and $R_{21}$ is hydroxy, being $\alpha$-hydroxy or $\beta$-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 $\alpha$-$R_i$;$\beta$-$R_j$, 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 $\alpha$-OH;$\beta$-$R_5$, 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 9$\beta$-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$\alpha\beta$,9$\beta$-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 $\beta$-hydrogen are characterized as "9-deoxy-2′,9$\alpha$-methano-3-oxa-4,5,6-trinor-3,7-(1′,3′-inter-phenylene)-$PGF_1$" compounds. Corresponding compounds wherein $R_{22}$ is $\alpha$-hydrogen are characterized as "9-deoxy-2′,9$\beta$-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′,9$\alpha$-methano-3-oxa-4,5,6-trinor-3,7-(1′,3′-inter-phenylene)-$PGF_1$" or "6a-oxo-9-deoxy-2′,9$\beta$-methano-3-oxa-4,5,6-trinor-3,7-(1′,3′-inter-phenylene)-$PGF_1$" depending on whether $R_{22}$ is $\alpha$-hydrogen or $\beta$-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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