FORM 25 (12) PATENT granted by (19) AP

AFRICAN REGIONAL INDUSTRIAL PROPERTY ORGANIZATION (ARIPO)

340

(11) A

(21) Application Number: AP/P/91/00278

(22) Filing Date: 10.06.91

(24) (45) Date of Grant & Publication: 13.05.94

(30) Priority Data:

(33) Country: US

(31) Number: 07/536,107

(32) Date: 11.06.90

(84) Designated States:

BW GM GH KE LS MW SD SZ UG ZM ZW

(73) Applicant (s):

BIOCHEM PHARMA INC.
2550 Daniel Johnson Boulevard
Suite 600 Laval
Quebec H7T 2LI
CANADA

(72) Inventor (s):

GIORGIO ATTARDO
8294 de l'Aiglon
St-Leonard Quebec
H1R 3M9
CANADA

(see overleaf)

(74) Representative:

GEORGE SEIRLIS & ASSOCIATES
P O BOX 3568
HARARE
ZIMBABWE

(51) International Patent Classification Int. Cl.[5] C07H 15/252, A61K 31/71, C07D 221/18

(54) Title: HETEROCYCLIC ANATHRACYCLINONE AND ANATHRACYCLINE ANALOGS

(57) Abstract

Heterocyclic Anthracyclinone and Anthracycline derivatives are described, which are useful in the treatment of cancer and tumors, such as breast cancer, leukemia, lung cancer, colon cancer, ovarian cancer, renal cancer, CNS cancer and melanoma. Pharmaceutical compositions and methods of preparing the compounds are also described.

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(56) Documents cited: JP-52-148079 engl. Abstract JP-52-1480881 engl. Abstract
US-J., Chemical Abstracts vol. 113, 1990, 115652

Inventors continued

2. BERNARD BELLEAU
431 Victoria Avenue
Westmount, Quebec
H3Y 2R3
CANADA

3. YAO CHANG XU
310 Gagne
Pierrefonds, Quebec
H8Y 1B2
CANADA

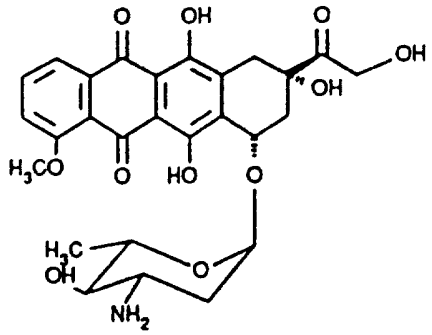
4. JEAN-FRANCOIS LAVALLEE
1212 Bleriot Chomedey Laval
Quebec
H7W 5G1
CANADA

5. RABINDRA N. REJ
2150 Mackay, apt. 1001
Montreal
Quebec
H3G 2M2
CANADA

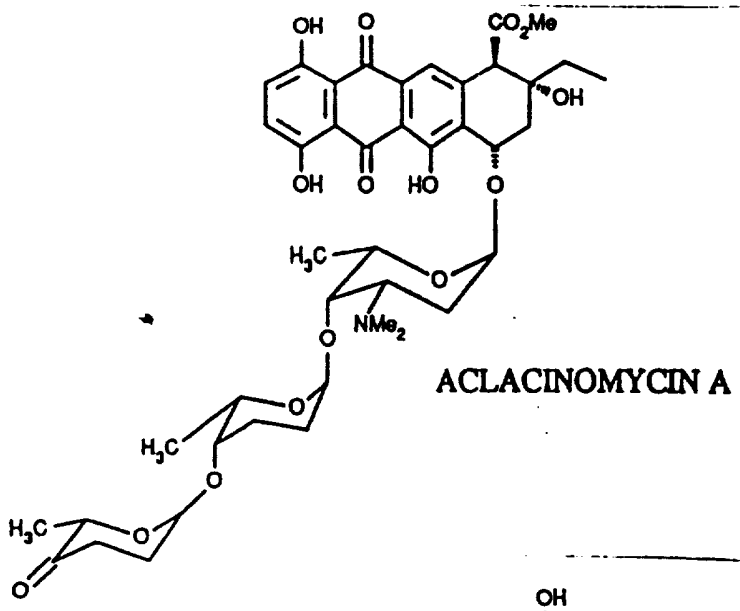
The usefulness of known anthracycline antibiotics is compromised by dose limiting toxicities such as myelosuppression (Crooke, S.K., Anthracyclines; Current Status and New Developments, Academic Press, N.Y. 1980) and cardiotoxicity (Olson, R.D. et al, Proc. Natl. Acad. Sci., USA 85 3585-3589, 1988 and references therein) as well as the resistance from treated tumors (Mimnaugh, E.G. et al, Cancer Research, 49, 8-15, 1989; McGrath, T. et al, Biochemical Pharmacology, 38 497-501, 1989). In view of the proven effectiveness of known anthracyclines in the treatment of cancer, efforts have been undertaken to develop anthracycline analogs with either an improved therapeutic index or with reduced cross-resistance.

Several thousands of anthracycline derivatives have been obtained either from streptomyces biosynthesis or via the semisynthetic modification of known natural anthracycline antibiotics (Arcamone, F., Doxorubicin, Academic Press, N.Y. 1980; Thomson, R.H., Naturally Occurring Quinones III: Recent Advances, Chapman and Hall, New York 1987; Anthracyclines: Current Status and New Developments, Academic Press, New York, 1980; Brown, J.R. and Iman, S.H., Recent Studies on Doxorubicin and its Analogues, Prog. Med. Chem. 21 170-236, 1984; Brown, J.R. Adriamycin and Related Anthracycline Antibiotics, Prog. Med. Chem., 15, 125-164, 1978). The majority of known anthracyclines show two types of structural differences: (i) the substitution pattern of the aglycone tetracyclic ring system, and (ii) the structure and number of glycosides attached at C-7 or

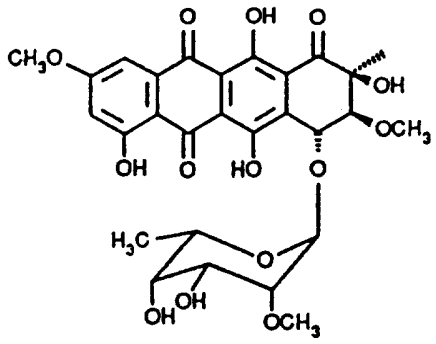
C-10 (doxorubicin numbering). Some examples of the structural diversity of anthracycline antibiotics are shown in Figure 1.



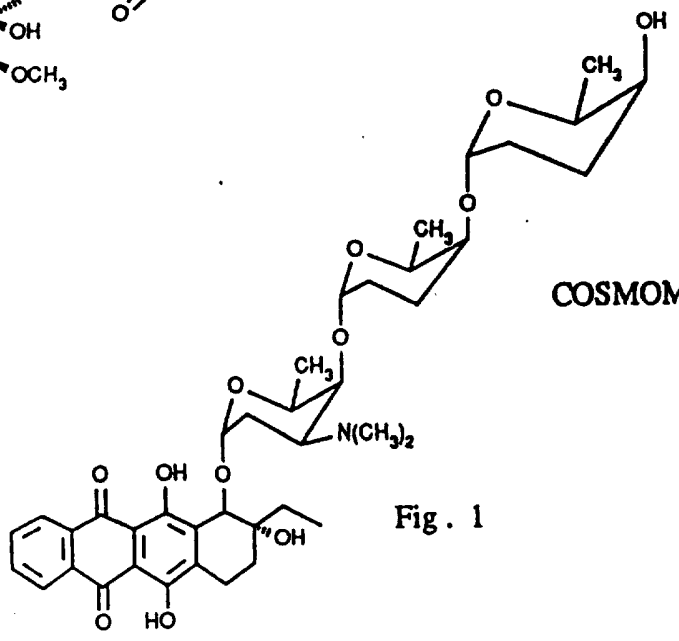
EPIRUBICIN



ACLACINOMYCIN A



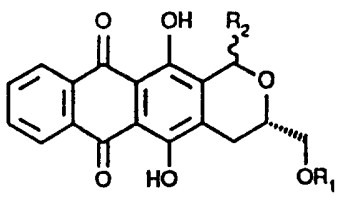
STEFFIMYCIN B



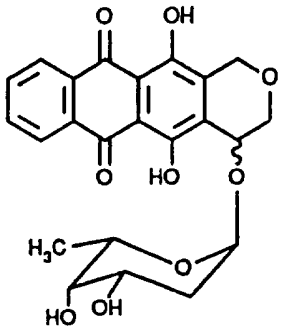
COSMOMYCIN A

Fig. 1

In contrast to the great number of derivatives obtained from these two kinds of structural modifications, there has been little effort towards the synthesis and biological evaluation of ring-A heteroanthracycline derivatives. Some 9-oxa-hetero-anthracyclines (3-5) were prepared by Koch et al but antitumor activity was not significant (Heterocycles, 26(2), 341-5, 1987; Heterocycles 26(4), 879-82, 1987). Mitsher et al found that N-(trifluoroacetyl)-4-demethoxy-9-azadaunorubicin (6) had no antitumor activity (J. Med. Chem., 29(7), 1277-81, 1986).



3 R_1 =H; R_2 =H,CH_3
4 R_1 =sugar; R_2 =H,CH_3



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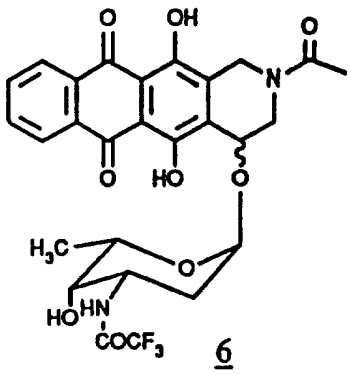

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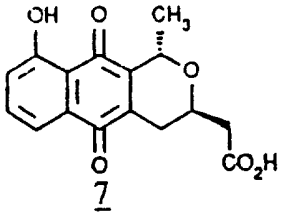
Pyranonaphthoquinones such as nanaomycin A (7) and kalafungin (8) occur naturally and show potent antibacterial as well as antifungal activity (Moore, H.W. and Czerniak, R., Medicinal Research Reviews, 1(3), 249-280, 1981 and references therein). Granaticin (9) has been reported to show antitumor activity (Chang, C.J., Floss, H.G., Soong, P. and Chang, C.T., J. Antibiot., 28, 156, 1975).



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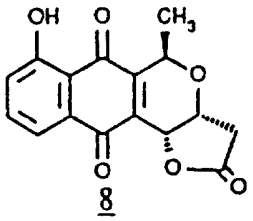

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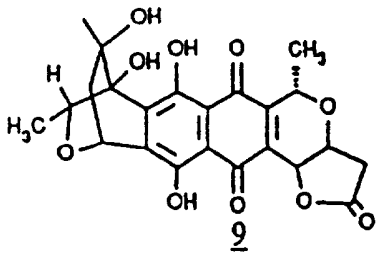

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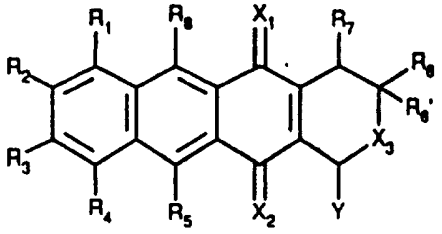
DESCRIPTION OF THE INVENTION

The present invention provides heteroanthracyclines which are structurally distinguished from the prior art compounds by the nature of ring A of the anthracyclinone moiety. More specifically, the compounds of the present invention are structurally distinguished from the prior art compounds by having an hetero atom at position 8 of the ring A of the anthracyclinone. This structurally distinct class of compounds exhibits therapeutic activity, in particular anticancer and antitumor activity, are active against some adriamycin-resistant tumor cells, and also may potentially display less myelosupression.

In one aspect of the invention, there is provided a compound of the formula (10):



10

wherein

X_1 and X_2 are independently selected from the group consisting of

O,

S,

C=N(R), wherein R is selected from the group consisting of

hydrogen,

C_{1-16} alkyl,

C_{1-16} acyl and,

C_{1-16} alkylamine,

X_3 is selected from the group consisting of

O,

S,

SO,

SO_2,

NO, and

NR, wherein R is selected from the group consisting of

C_{1-16} acyl,

C_{1-16} alkyl,

C_{1-16} aryl,

C_{1-16} haloacyl, and

hydrogen;

R_1, R_2, R_3, R_4, R_5 and R_8 are independently selected from the group consisting of

hydrogen,

hydroxyl,

C_{1-16} alkyl,

C_{1-16} alkoxyl,

C_{3-8} cycloalkyl,

tosyl,

triflate,

trifluoroacetate,

halogen,

nitro,

cyano,

C_{1-16} acyl,

C_{1-16} arylacyl,

aminoalkylaminoalcohol of formula $NH(CH_2)_NNH(CH_2)_mOH$ where n and m independently range from 1 to 4,

aminoalkylaminoalkylhalide of formula $NH(CH_2)_nNH(CH_2)_mX$ where n and m independently range from 1 to 4 and X is a halogen,

amino which may be unsubstituted or mono- or di-substituted by C_{1-8} alkyl, C_{3-8} cycloalkyl, acyl, trifluoroacyl, aralkyl or aryl, C_{1-8} alkenyl, C_{1-8} alkynyl,

halaoalkylnitrosureido of the formula $NH(CO)N(NO)(CH_2)_n\ CH_2X$, wherein n is 0 to 4 and X is a halogen,

thiol, and

a group of the formula -O-C(R)=O wherein R is selected from the group consisting of

hydrogen,
C_{1-16} alkyl,
C_{3-8} cycloalkyl,
alkoxyalkyl,
aralkyl,
araloxyalkyl,
aryloxyalkyl and
aryl;

R_6 is selected from the group consisting of
hydrogen,
C_{1-16} alkyl,
C_{3-8} cycloalkyl,
acyl of the formula -C(R)=O, or its dioxolane or dioxane ketal wherein R is selected from the group consisting of
hydrogen,
C_{1-16} alkyl,
C_{3-8} cycloalkyl,
hydroxyalkyl,
alkoxyalkyl,
araloxyalkyl,
acyloxyalkyl,
amino which may be unsubstituted or mono- or di-substituted by C_{1-8} alkyl, C_{3-8} cycloalkyl, acyl, trifluoroacyl, aralkyl or aryl, and a naturally occurring amino acid, for example alanine, arginine, cysteine, glycine, leucine, lysine, methionine and the like, or a synthetic amino acid;
a group of the formula $-C(R)(OC_{1-5}\ alkyl)_2$ where R is as defined above
a group of the formula -C(OR)=O, wherein R is selected from the group consisting of
hydrogen,

C_{1-16} alkyl,
C_{3-8} cycloalkyl,
hydroxyalkyl,
alkoxyalkyl,
aryloxyalkyl,
araloxyalkyl,
aryl and
aralkyl;

a group of the formula $-CH_2C(OR)=O$, wherein R is selected from the group consisting of

hydrogen,
C_{1-16} alkyl,
C_{3-8} cycloalkyl,
hydroxyalkyl,
alkoxyalkyl,
aryloxyalkyl,
araloxyalkyl,
aryl,
aralkyl, and
amino, which may be unsubstituted, mono- or di-substituted by C_{1-8} alkyl, C_{3-8} cycloalkyl, acyl, trifluoroacyl, aralkyl or aryl;

R_6' is selected from the group consisting of

hydrogen,
C_{1-16} alkyl,
halogen,
amino,
hydroxy,
C_{1-16} alkoxy,
thiol,
cyano,

sulfide,

acyl of the formula -C(R)=O, wherein R is selected from the group of

hydrogen,

C_{1-16} alkyl,

C_{3-8} cycloalkyl,

hydroxyalkyl,

araloxyalkyl,

alkoxyalkyl,

acyloxyalkyl,

amino which may be unsubstituted or mono- or di-substituted by C_{1-8} alkyl, C_{3-8} cycloalkyl, acyl, trifluoroacyl, aralkyl or aryl, and a naturally occuring amino acid, for example alanine, arginine, cysteine, glycine, leucine, lysine, methionine and the like, or a synthetic amino acid;

A group of the formula -C(OR)=O, wherein R is selected from the group consisting of

hydrogen,

C_{1-16} alkyl,

C_{3-8} cycloalkyl,

hydroxyalkyl,

alkoxyalkyl,

aryloxyalkyl,

araloxyalkyl,

aryl and

aralkyl;

C_{1-16} alkenyl

Y and R_7 are independently selected from the group consisting of

hydrogen,
halogen,
hydroxyl,
C_{1-16} alkoxyl,
C_{1-16} alkyl,
C_{2-16} acetylenyl,
C_{3-8} cycloalkyl,
C_{2-16} alkenyl,
cyano,
a group of the formula -O-C(R)=O, wherein R is selected from the group consisting of
hydrogen,
C_{1-16} alkyl,
C_{3-8} cycloalkyl, and
alkoxyalkyl,
aryl;
an acyl of the formula -C(R)=O, wherein R is selected from the group consisting of
hydrogen,
thiol,
C_{1-16} thioalkyl,
C_{1-16} alkyl,
C_{3-8} cycloalkyl,
hydroxyalkyl,
alkoxyalkyl,
araloxyalkyl,
acyloxyalkyl,
amino which may be unsubstituted or mono- or di-substituted, and a naturally occurring amino acid as defined above or a synthetic amino acid;
a group of the formula -C(OR)=O, wherein R is selected from the group consisting of

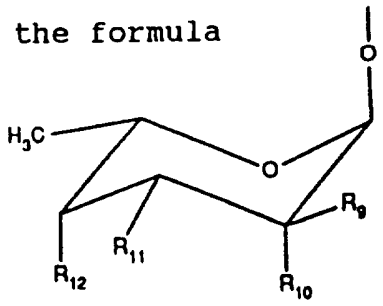
hydrogen,

C_{1-16} alkyl, and

C_{3-8} cycloalkyl; and

mono or oligosaccharides commonly present in other anthracyclines, for example one or more sugars selected from rhodosamine, cinerulose-B, L-cinerulose, D-cinerulose, cinerulose-A, amicetose, aculose, rednose, rhodinose, 2-deoxyfucose,

and a saccharide of the formula



wherein

R_9 and R_{10} are independently selected from the group consisting of

hydrogen,

halogen,

hydroxy,

acetoxy,

C_{1-16} alkoxy,

C_{1-16} alkyl,

C_{3-8} cycloalkyl, and

thiol;

R_{11} is selected from the group consisting of

amino, which may be unsubstituted or mono or di-substituted by C_{1-8} alkyl, C_{3-8} cycloalkyl, acyl, trifluoroacyl, aralkyl or aryl and a naturally occuring amino acid, for example alanine, arginine, cysteine, glycine, leucine, lysine,

methionine and the like, or a syntehtic amino acid;
mono or dibenzylated amino,
acylated amino,
trifluoroacylated amino,
morpholino,
cyano substituted morpholino,
mono-, di-, tri- or tetra-methoxy substituted morpholino,
mono-, di, tri-or tetra-acetoxy substituted morpholino,
hydroxyl,
hydrogen,
halogen,
acetoxy,
C_{1-16} alkoxyl,
C_{3-8} cycloalkyl,
thiol,
sulfide,
a group of the formula $NH(CH_2)_NCH(OR)_2$, wherein R is independently selected from the group consisting of a C_{1-16} alkyl, C_{1-16} acyl or C_{7-16} aroyl and wherein n is 0 to 5,
chloroalkylnitrosoureido of the formula $NH(CO)N(NO)(CH_2)_nCH_2Cl$, wherein n is 0 to 4;

R_{12} is selected from the group consisting of
hydrogen,
hydroxyl or its tetrahydropranyl ether (-OTHP),
halogen,
mono or oligosaccharides commonly present in other anthracyclines such as those defined above for R_7,

amino,
mono or dialkylated amino in which each alkyl contains 1 to 16 carbon atoms,
C_{1-16} alkoxy,
C_{3-8} cycloalkyl,
benzoate which may be unsubstituted or substituted with nitro, for example p-nitrobenzoate,
acetoxy, and
trifluoroacetoxy.
chloroalkyl-nitrosoureido as defined above for R_{11}

Preferred compounds of formula (10) are those wherein

X_1, and X_2 are independently selected from the group consisting of
O,
S, and
NH;

X_3 is selected from the group consisting of
O,
S,
SO,
SO_2,
NH, and
NO;

R_1, R_2, R_3, R_4, R_5 and R_8 are independently selected from the group consisting of
hydrogen,
hydroxyl,
C_{1-4} alkoxyl,
tosyl,
triflate,

fluorine,
chlorine,
aminoalkylaminoalcohol of formula $NH(CH_2)_nNH(CH_2)_mOH$ where n and m independently range from 1 to 3,
aminoalkylaminoalkylchloride of formula $NH(CH_2)_nNH(CH_2)_mCl$ where n and m independently range from 1 to 3.
amino,
chloroalkylnitrosoureido of the formula $NH(CO)N(NO)(CH_2)_n\ CH_2\ Cl$, wherein n is 0 to 4, and
a group of the formula -O-C(R)=O, wherein R is selected from the group consisting of
hydrogen,
C_{1-6} alkyl,
and aryl;

R_6 is selected from the group consisting of
hydrogen,
C_{1-4} alkyl,
acyl of the formula -C(R)=O, wherein R is selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
hydroxylalkyl,
alkoxyalkyl,
acyloxyalkyl and
amino which may be unsubstituted or mono- or di-substituted with C_{1-8} alkyl, C_{3-8} cycloalkyl, acyl, trifluoroacyl, aralkyl or aryl;
a group of the formula -C(OR)=O, wherein R is

selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
aryl,
aralkyl; and
a group of the formula $-CH_2C(OR)=O$, wherein R is selected from the group consisting of
hydrogen,
straight or branched C_{1-8} alkyl, and
amino which may be unsubstituted or mono- or di-substituted with C_{1-8} alkyl, C_{3-8} cycloalkyl, acyl, trifluoroacyl, aralkyl or aryl;

R_6' is selected from the group consisting of
hydrogen,
fluorine,
amino,
C_{1-4} alkoxy,
sulfide,
acyl of the formula $-C(R)=O$, where R is selected from the group of
hydrogen,
C_{1-8} alkyl,
hydroxyalkyl,
acyloxyalkyl,
amino,
cyano,
a group of the formula $-C(OR)=O$, wherein R is selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
aryl,
C_{1-8} alkenyl;

Y and R_7 are independently selected from the group consisting of

hydrogen,

halogen,

hydroxyl,

C_{1-8} alkoxy,

C_{2-8} acetylenyl,

C_{2-8} alkenyl,

cyano,

a group of the formula -O-C(R)=O, wherein R is selected from the group consisting of

hydrogen, and

C_{1-8} alkyl;

acyl of the formula -C(R)=O, wherein R is selected from the group consisting of

hydrogen,

thiol,

C_{1-8} alkyl,

hydroxyalkyl,

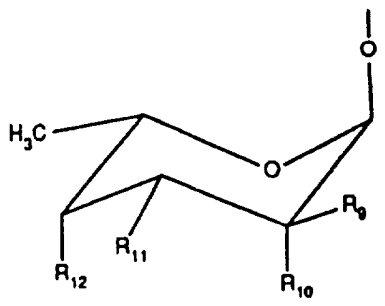
amino;

a group of the formula -C(OR)=O, wherein R is selected from the group consisting of

hydrogen, and

C_{1-8}alkyl,

and a saccharide of formula



wherein

R_9 and R_{10} are independently selected from the group

consisting of
hydrogen,
fluorine,
chlorine, and
hydroxyl;

R_{11} is selected from the group consisting of
amino which may be unsubstituted or mono- or di-substituted with C_{1-8} alkyl, C_{3-8} cycloalkyl, acyl, trifluoroacyl, aralkyl or aryl;
morpholino,
cyano substituted morpholino,
mono-, di-, tri-, or tetra-methoxy substituted morpholino,
hydroxyl,
mono or dialkylated amino with 1 to 16 carbons,
C_{1-8} alkoxyl,
a group of the formula $NH(CH_2)_NCH(OR)_2$ wherein R is independently selected from a group consisting of C_{1-8} alkyl, C_{1-8} acyl or C_{7-12} aroyl and wherein n is 1 to 5;
chloroalkylnitrosoureido of the formula $NH(CO)N(NO)(CH_2)_nCH_2Cl$ wherein n is 0 to 4, and
fluorine; and

R_{12} is selected from the group consisting of
hydroxyl or its tetrahydopyranyl ether,
halogen,
mono or oligosaccharide commonly present in other anthracyclines, for example one or more sugars selected from rhodosamine,

cinerulose-B, L-cinerulose, D-cinerulose,
cinerulose A, amicetose, aculose, rednose,
rhodinose, 2-deoxyfucose, daunosamine and
trifluoroacetyldaunosamine,
amino,
mono or dimethylated amino,
C_{1-8} alkoxy,
benzoate,
p-nitrobenzoate,
acetoxy and
trifluoroacetoxy.

More preferred compounds of formula (10) are those wherein
X_1, and X_2, are independently selected from the group consisting of
O, and
NH;
X_3 is selected from the group consisting of
O,
S,
SO,
NH,
NO;
R_1, R_2, R_3, R_4, R_5 and R_8 are independently selected from the group consisting of
hydrogen,
hydroxy,
methoxy,
aminoethylaminoethanol
aminoethylaminoethylchloride
chloroalkylnitrosoureido of the formula
$NH(CO)N(NO)(CH_2)_nCH_2Cl$, wherein n is 0 to 2,

amino, and
fluorine;

R_6 is selected from the group consisting of
C_{1-4} alkyl,
acyl of the formula -C(R)=O, wherein R is selected from the group consisting of
methyl,
hydroxymethyl,
acyloxymethyl and
amino;
a group of the formula -C(OR)=O, wherein R is selected from the group consisting of
hydrogen,
methyl and
ethyl;
a group of the formula $-CH_2C(OR)=O$, wherein R is selected from the group consisting of
hydrogen,
methyl and
ethyl;
R_6' is selected from the group consisting of
hydrogen,
fluorine,
amino,
methoxy,
acyl of the formula -C(R)=O, wherein R is selected from the group of
hydrogen,
C_{1-5} alkyl,
hydroxyalkyl,
amino,
cyano,

a group of the formula -C(OR)=0, wherein R is selected from the group consisting of

hydrogen,

C_{1-5}, alkyl,

aryl,

C_{1-4}, alkenyl;

Y and R_7 are independently selected from the group consisting of

hydrogen,

halogen,

hydroxy,

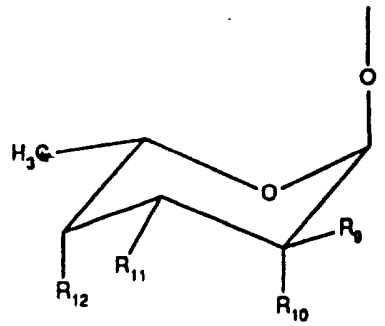
methoxy,

cyano,

acetate,

acetyl and

a saccharide of formula



wherein

R_9 and R_{10} are independently selected from the group consisting of

hydrogen and

fluorine;

R_{11} is selected from the group consisting of

amino,

dimethylamino,

trifluoroacetamido,
morpholino,
cyano substituted morpholino,
mono-, di-, tri-, or tetra-methoxy substitiuted morpholino,
a group of the formula $NH(CH_2)_NCH(OR)_2$ wherein R is selected from a group consisting of C_{1-4} alkyl C_{1-4} acyl or C_{7-8} aroyl and wherein N is 2 to 5,
chloroalkylnitrosoureido of the formula $NH(CO)N(NO)(CH_2)_nCH_2Cl$, wherein n is 0 to 4, and
hydroxyl; and

R_{12} is selected from the group consisting of
hydroxyl or its tetrahydopyranyl ether,
benzoate,
p-nitrobenzoate,
amino, and
fluorine.

Further preferred compounds of the formula (10) are those wherein
X_1 and X_2 are both oxygen;
X_3 is selected from the group consisting of
O,
S,
SO,
NH,
NO;

R_1, R_2, R_3 and R_4 each are hydrogen;

R_5 and R_8 are independently selected from the group

consisting of

hydrogen,

hydroxyl,

amino,

aminoethylaminoethanol,

R_6 is selected from the group consisting of

methyl,

ethyl,

acyl of the formula -C(R)=O, or its dioxolane or dioxane ketal wherein R is selected from the group consisting of

methyl,

hydroxymethyl

acetoxymethyl, and

amino;

a group of the formula C(OR)=O, wherein R is selected from the group consisting of

hydrogen and

methyl; and

a group of the formula $-CH_2C(OR)=O$, wherein R is selected form the group consisting of

hydrogen and

methyl;

R_6' is selected from the group consisting of

hydrogen,

fluorine,

amino,

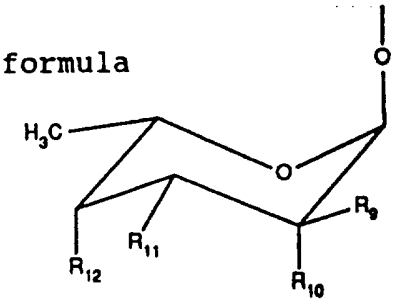
cyano, and

a group of the formula -C(OR)=O, wherein R is selected from the group consisting of

C_{1-4} alkyl,

Y and R_7 are independently selected from the group

consisting of
hydrogen,
hydroxyl,
bromine,
chlorine,
cyano,
acetate,
acetyl and
a saccharide of formula



wherein
R_9 and R_{10} are independently selected from
hydrogen and
fluorine;

R_{11} is selected from
amino,
dimethylamino,
trifluoroacetamido,
morpholino,
cyano substituted morpholino,
mono-, di-, tri- or tetra-methoxy substituted morpholino and
a group of the formula $NH(CH_2)_NCH(OR)_2$ wherein R is selected from a group consisting of methyl, acyl or benzoyl and wherein N is 3 to 5,
chloroalkylnitrosoureido of the formula $NH(CO)N(NO)(CH_2)_nCH_2Cl$, wherein n is 0 to 4, and

R_{12} is selected from hydroxyl, benzoate and p-nitrobenzoate.

The term "alkyl" as employed herein includes both straight and branched chain radicals of up to 16 carbons, for example methyl, ethyl, propyl, isopropyl, butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, the various branched chain isomers thereof, as well as such groups including one or more halo substituent, such as F, Cl, Br, I or CF_3, an alkoxy substituent, an aryl substituent, an alkyl-aryl substituent, a haloaryl substituent, a cycloalkyl substituent or an alkylcycloalkyl substituent.

The term "cycloalkyl" as used herein means a cycloalkyl group having 3 to 8 carbons, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclopentylmethyl, cyclohexylmethyl, cyclohexylethyl, cycloheptyl and cyclooctyl.

The term "aryl" as employed herein refers to monocyclic or bicyclic aromatic groups containing from 6 to 10 carbons in the ring portion, such as phenyl, naphthyl, substituted phenyl or substituted naphthyl, wherein the substituent on either the phenyl or naphthyl may be for example C_{1-4} alkyl, halogen, C_{1-4} alkoxy or nitro.

The term "halogen" as used herein means chlorine, bromine, fluorine or iodine.

The term "aralkyl" as used herein refers to alkyl groups as discussed above having an aryl substituent, such as benzyl, p-nitrobenzyl, phenethyl, diphenylmethyl, and triphenylmethyl.

The term "aroyl" as used herein refers to a group of the formula -COAr wherein Ar denotes an "aryl" group as defined above.

The term "alkoxy" or "aralkoxy" as used herein includes any of the above alkyl or aralkyl groups linked to an oxygen atom.

The term "alkoxyalkyl" as used herein means any alkyl as discussed above linked to any alkoxy as discussed above, for example methoxymethyl.

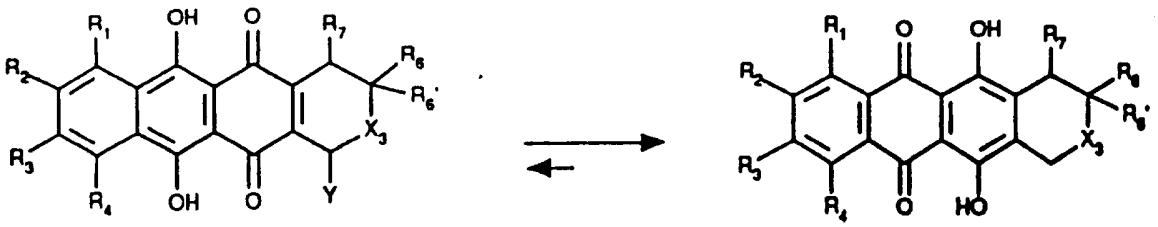
The term "aryloxyalkyl" as used herein means any alkyl as discussed above linked to an aryl as discussed above by an oxygen atom, for example phenoxymethyl.

The term "araloxyalkyl" as used herein means an aralkyl as discussed above linked to an alkyl as discussed above by an oxygen atom, for example benzyloxymethyl.

The term "acyloxyalkyl" as used herein means an C_{1-8}acyl group linked to an alkyl group as discussed above by an oxygen atom, for example acetoxymethyl.

The term "hydroxyalkyl" as used herein means an alkyl group as discussed above bonded to a hydroxyl group, for example hydroxymethyl.

It will be appreciated by those skilled in the art that when R_5=R_8= hydroxyl and X_1=X_2=O that compounds of formula (10) exist in the form of the thermodynamically favored tautomers of formula (11). Therefore, compounds of formula (11) are included within the scope of the invention.



10

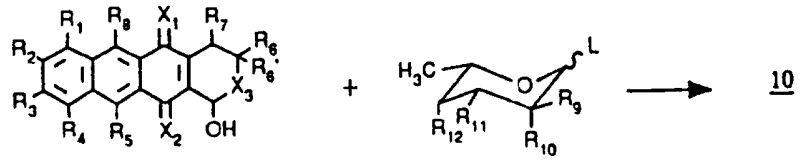
($X_1 = X_2 = O$ and $R_5 = R_8 = OH$)

11

This invention also includes all the possible isomers and mixtures thereof, including diastereoisomeric mixtures and racemic mixtures, resulting from the possible combination of R or S stereochemical centers, when pertinent, at C-7, C-9 and C-10 as well as in all the chiral centers present in the sugar moiety.

This invention also comprises novel compounds which are prepared as intermediates or precursors of compounds of formulas (10) and (11). Such intermediate compounds are described hereinafter in connection with processes of preparing compounds of formulas (10) and (11).

The compounds of formula (10) can be prepared by the process illustrated in Reaction Scheme I.



12

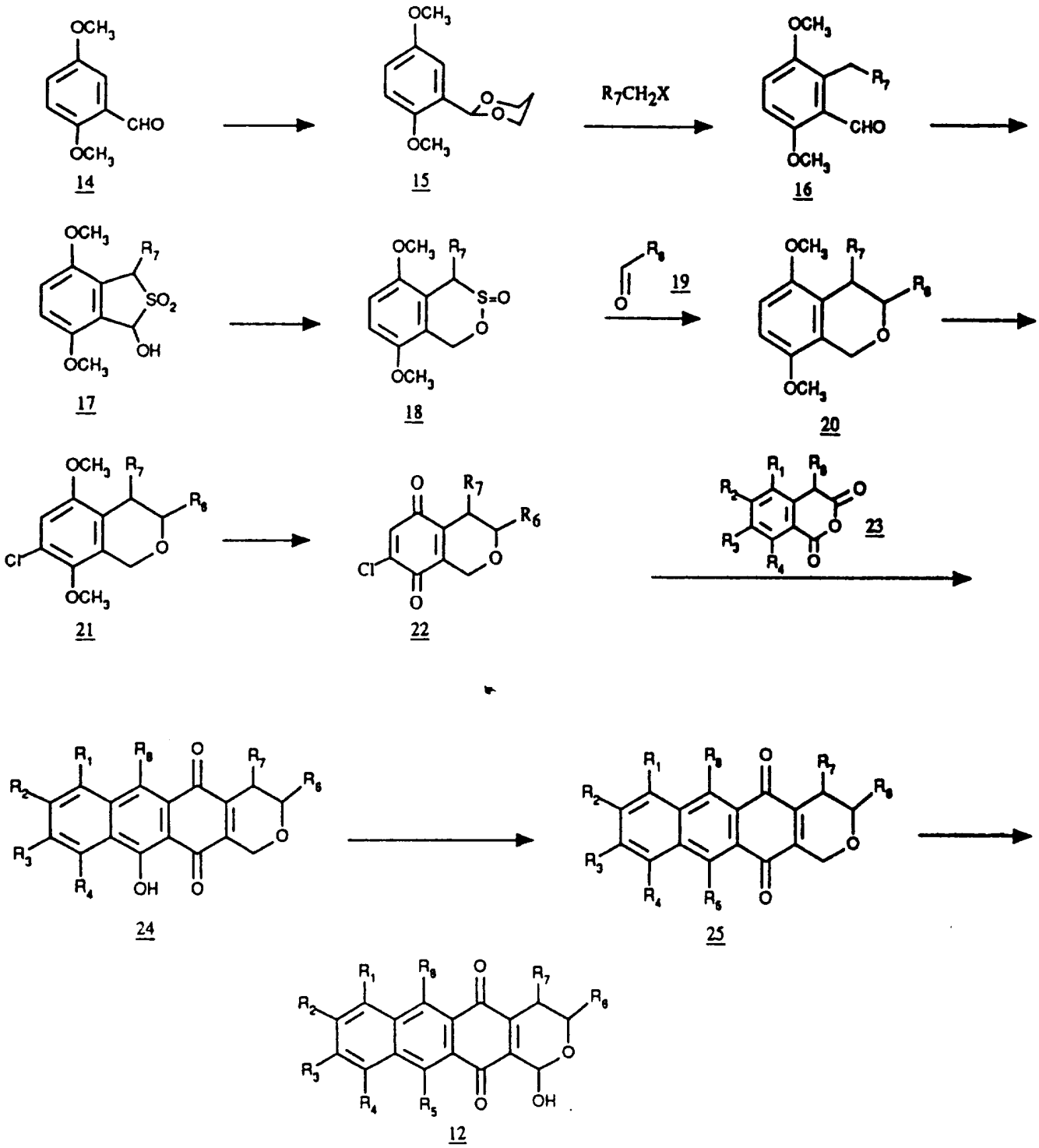
13

Heteroanthracyclines of general formula (10) in which Y is a saccharide are best prepared by using scheme I. With reference to Reaction Scheme I, an aglycone of formula (12) in which R_1 to R_8 are as defined herein is reacted with a sugar derivative of formula (13) in which R_9 to R_{12} are as defined herein and L is a displaceable atom or group. Suitable groups L include halogen, for example iodine, bromine or chlorine, an unsubstituted or substituted benzoyl group such as p-nitrobenzoyl, and -OR or -SR, where R is an unsubstituted or substituted alkyl group, for example a C_{1-16} alkyl group such as methyl, ethyl or butyl, or R is an unsubstituted or substituted acyl group such as a C_{1-16} acyl group such as acetyl, or R is an unsubstituted or substituted aryl group. Such sugars are obtained by derivatizing known saccharides of the family of anthracycline antibiotics which are available from commercial or natural sources, (see for example, Monneret, C., Martini, A., Pais, M., Carbohydrate Research, 166, 59-70, 1987 and references therein; Acton, E.M., Tong, G.L., Mosher, C.W., and Wolgemuth, R.L., J. Med. Chem. 27, 638-645, 1984 and references therein; Arcamone F., Cancer Research, 45, 5995-5999, 1985 and references therein).

The aglycone of formula (12) is typically reacted with the appropriate sugar derivative of formula (13) in a compatible solvent such as methylene chloride using a Lewis acid such as titanium tetrachloride, stannic chloride, of trimethylsilyltrifluoromethane-sulfonate. Alternatively, as it is known in the art of anthracycline chemistry, when the leaving group of the sugar moiety is a halogen, the Koenigs-Knorr glycosidation or its modification may be used.

A method of preparing the compounds of formula (12) in which X_1, X_2, X_3 = O and R_6' = hydrogen, is illustrated in Reaction Scheme II.

Reaction Scheme II



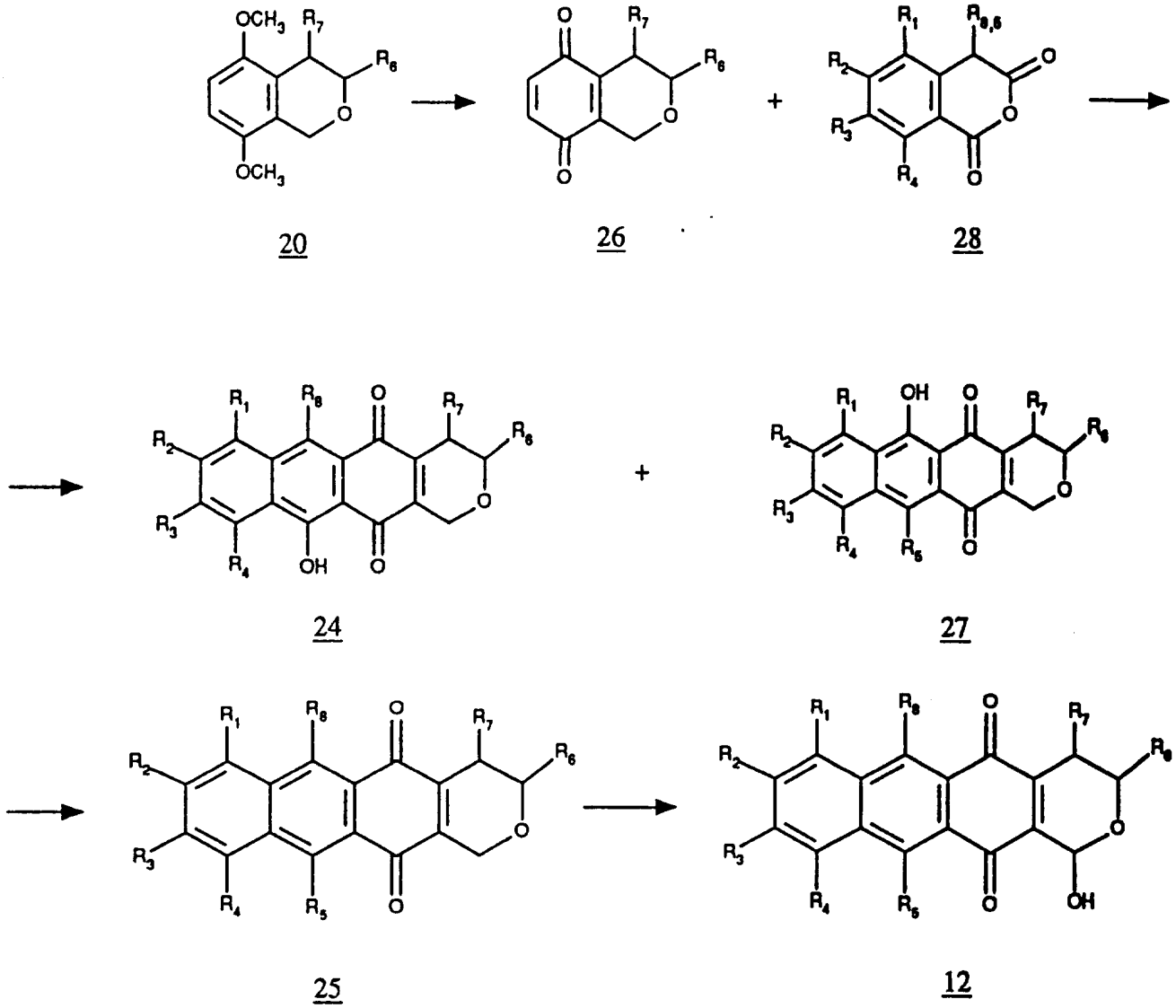
With reference to Reaction Scheme II, 2,5-dimethoxyben-zaldehyde dioxane acetal (15) can be prepared by treating at reflux 2,5-dimethoxybenzaldehyde (14) with 1,3-propanediol in benzene or any other suitable solvent and with an acid catalyst such as p-toluenesulfonic acid. The dioxane acetal (15) can then be treated with an alkyl lithium such as n-butyllithium and the lithio salt reacted with an appropriate alkyl halide of the formula R_7CH_2X, wherein X is halogen and R_7 is as defined above, but compatible with the necessary reaction conditions. In the event that R_7 is not compatible, functional group interconversion can be carried out at a latter step by using methods which are well known by one familiar with the art of organic synthesis.

Subsequent aqueous acidic treatment can lead to an appropriate 2,5-dimethoxy-6-alkylbenzaldehyde such as (16). Photochemical irradiation of an intermediate such as (16) in a solution of SO_2 in an aryl solvent such as benzene can give a dihydrothiophene-2,2-dioxide of formula (17) which can then be reduced with a borohydride. Following acidic treatment, a δ-sultine of formula (18) can be obtained. This intermediate can then be coupled via cyclocondensation with an appropriately functionalized aldehyde (19) and consequently yield dimethoxyisochroman intermediates such as (20). The intermediates (20) can subsequently be chlorinated with an hypochlorite such as t-butylhypochlorite to give compounds of formula (21). Oxidative demethylation of (21) with an adequate oxidant such as ceric ammonium nitrate can give chloropyranoquinones of formula (22). These quinones can then be coupled under basic conditions with adequately functionalized homophthalic anhydrides such as (23) to give pyranoquinone tetracyclic derivatives of formula (24). The

free phenol can then be protected to give tetracyclic compounds of the general formula (25). Tetracyclic derivative (25) can then be brominated with a free radical brominating agent such as n-bromosuccinimide in the presence of an initiator such as UV light and in a chlorinated solvent such as carbon tetrachloride. The resulting unstable bromides can then be treated directly with an aqueous-ethereal solvent system to yield the pyrano-tetracyclic aglycones of formula (12). The aglycones of formula (12) can further be transformed to a variety of structures by using synthetic methodologies well understood in the art of anthracycline synthesis. Any functional group interconversion or removal of protecting groups is preferentially carried out under neutral or basic conditions at this stage or later in the synthesis, as convenient.

A variation for preparing the compounds of formula (12) is illustrated in Reaction Scheme III.

Reaction Scheme III



With reference to Reaction Scheme III, dimethoxy-isochroman intermediates such as (20) can be directly oxidatively demethylated with an oxidizing reagent such as ceric ammonium nitrate in a polar solvent system such as acetonitrile in water. The resulting pyranoquinones of formula (26) can then be coupled with appropriately functionalized homophthalic anhydrides (23) in an aprotic solvent with basic catalysis, preferentially lithium diisopropylamide or sodium hydride. Tetracyclic derivative (27) can be separated from (24). The free phenol can then be protected to give compounds of the general formula (25). Bromination and solvolysis as described can give the aglycones of formula (12).

Preferred processes for the preparation of the compounds of formula (12) are illustrated in reaction Scheme IV. In route a of Scheme IV, the lithio salt, obtained after treatment of 2,5-dimethoxybenzaldehyde dioxane acetal (15) with an alkyl lithium, is reacted with an epoxide of general formula (31) optionally in the presence of a Lewis acid such as boron trifluoride etherate to give the adduct of formula (32).

Route b represents an alternative approach for the preparation of adduct (32). Consequently, the addition of an aldehyde of general formula (28) to the lithio salt of 2,5-dimethoxybenzaldehydedioxane acetal (15) can give an adduct of formula (29). In aldehyde (28), R'_1 is a protecting group, which includes, but is not limited to, methoxymethyl, methoxyethyl, methyl, benzyl, trityl, t-butyldimethylsilyl, t-butyldiphenylsilyl or other groups conveniently used for the protection of alcohols in the art of organic synthesis. The hydroxyl in formula (29) can be transformed to a variety of functionalities by using general methods obvious to those familiar with organic

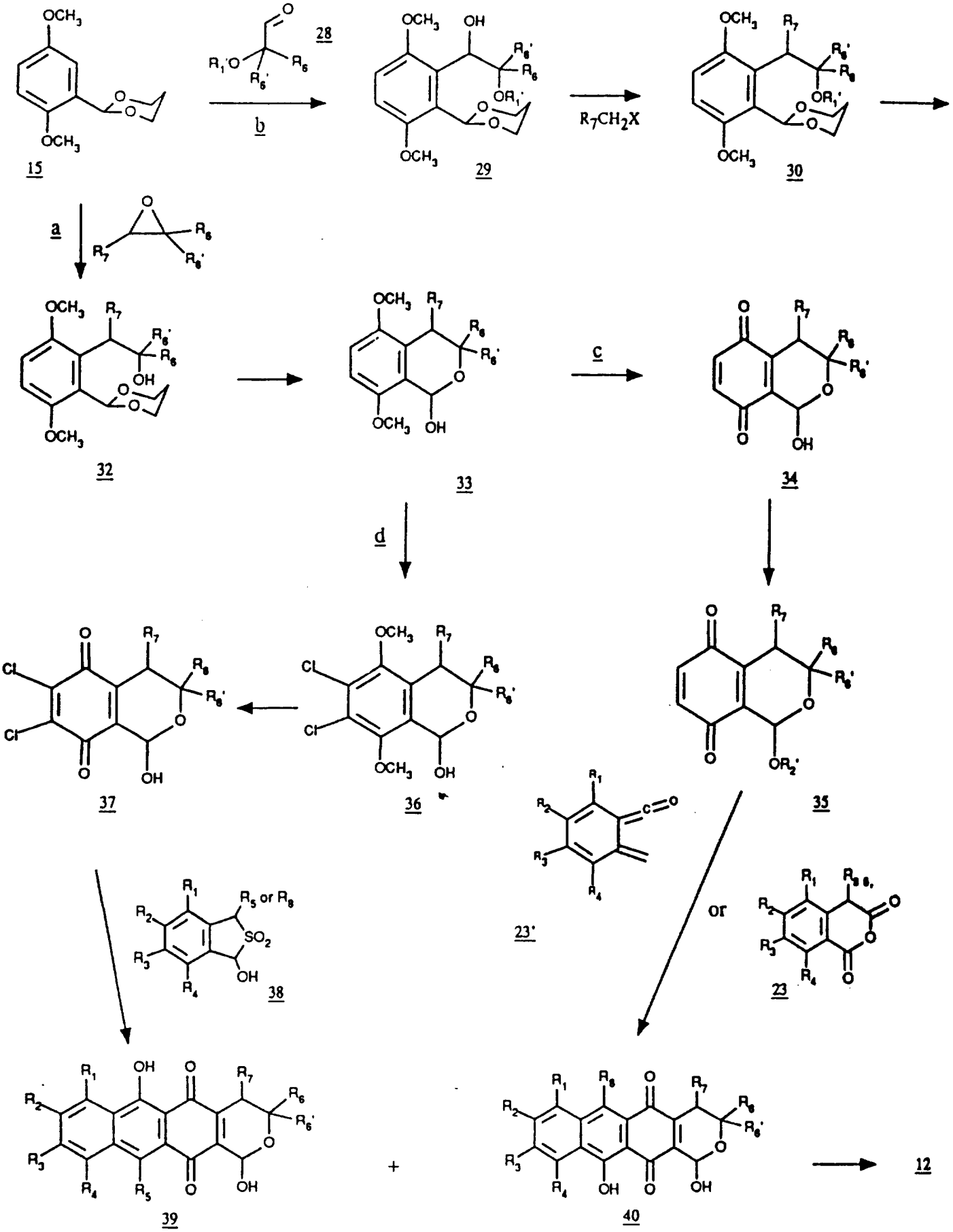
synthesis. Therefore, compounds of formula (30) can be obtained which upon deprotection of the secondary protected alcohol, by using known methods, yield the desired substituted benzaldehydedioxane acetal adduct (32).

The adduct of formula (32) is then cyclized in the presence of a mild aqueous acid to give 1-hydroxyisochroman of the formula (33).

The tetracyclic aglycones (39) and (40) can be prepared according to route c. Pyranoquinones of formula (34) are prepared by oxidizing isochromans of formula (33) with an agent such as silver oxide or ceric ammonium nitrate. Quinones of formula (35), in which the hydroxyl has been protected with a group R'_2, selected but not limited to, methyl, ethyl, methoxymethyl, methoxyethyl, trimethylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, benzyl, p-nitrobenzyl and trityl, can then be added to an homophthalic anhydride of formula (23) in the presence of strong base, or to a benzomonoketene of formula (23') under U.V. irradiation (Krohn K., et al, Liebigs Ann. Chem. 943-948 [1988]), to yield, after deprotection, the tetracyclic aglycones of general structures (39) and (40).

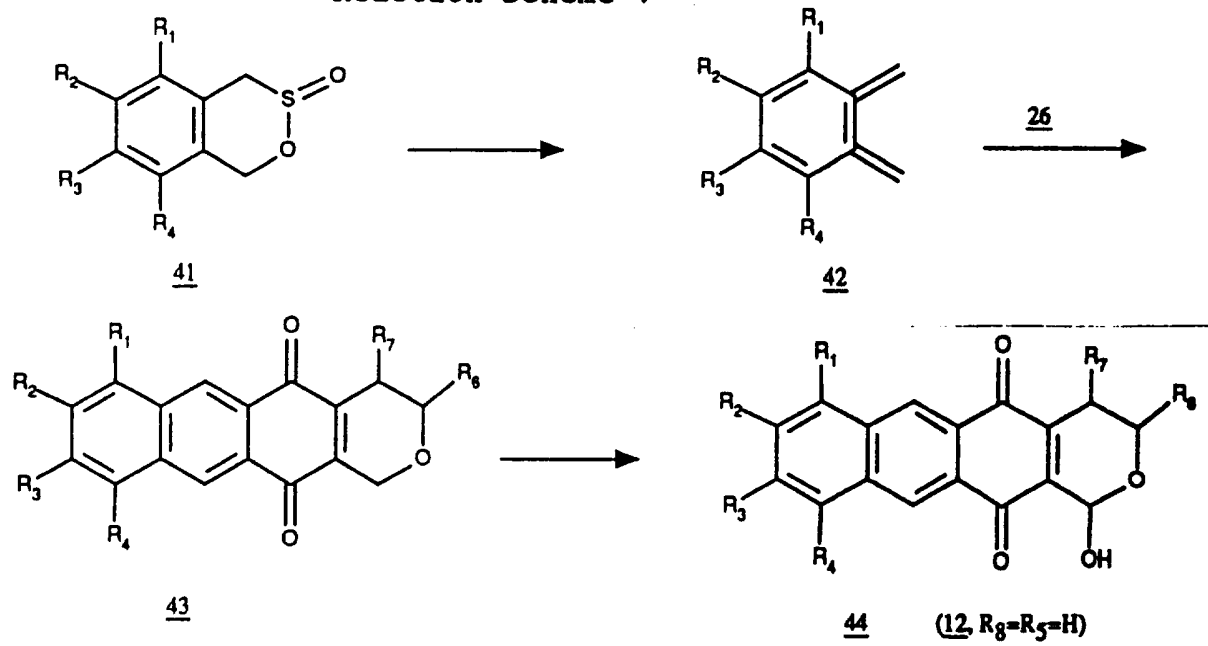
The tetracyclic aglycones (39) and (40) can also be prepared according to route d from isochroman (33) which after bis chlorination with a reagent such as t-butyl hypochlorite gives isochromans of formula (36). Subsequent oxidation with an agent such as ceric ammonium nitrate yields bischloropyranoquinones of formula (37). Addition of these quinones to o-quinodimethanes, generated thermolytically from benzosulfones such as (38), can give tetracyclic aglycones of formula (39) and (40). Compounds of the formula (12) are then accessible from these aglycones through functional group interconversion of the phenol group.

Reaction Scheme IV



A method of preparing compounds of formula (12) wherein R_8=R_5=H, is illustrated in Reaction Scheme V.

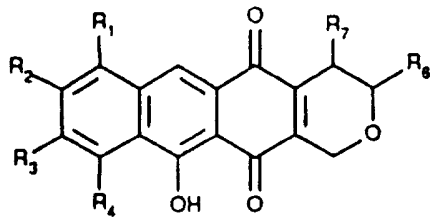
Reaction Scheme V



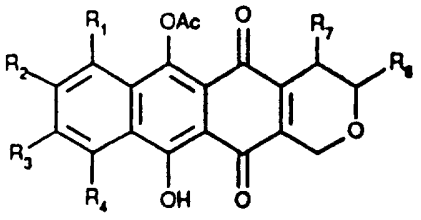
With reference to Reaction Scheme V, the cycloaddition reaction between an o-quinodimethane reactive intermediate (42), which can be generated by heating a precursor such as δ-sultine (41) (prepared by the method described for compound (18) in Reaction Scheme II), and a pyranoquinone such as (26) can yield pyranoquinone structures such as (43), after consecutive treatment with silica gel. Bromination and solvolysis as described for intermediate (23) can give pyranoquinone aglycones with no substituents on ring C such as (44).

The process for the preparation of compounds of formula (10) in which R_5=R_8=OH, which tautomerizes into compounds of formula (11), is illustrated in Reaction Scheme VI.

Reaction scheme VI



45 (24 , R_8 = H)



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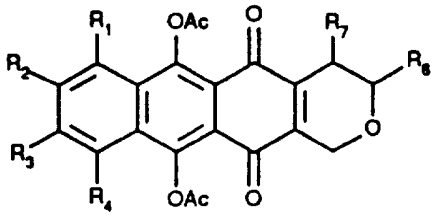

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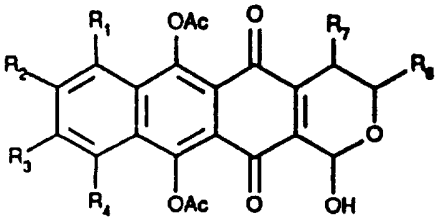

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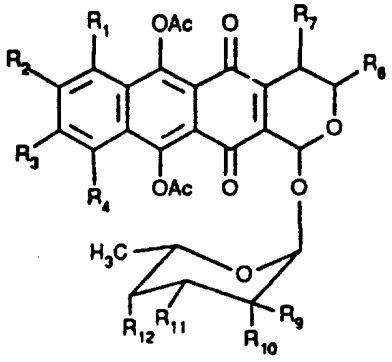

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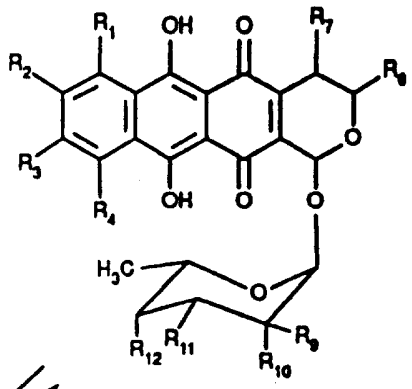
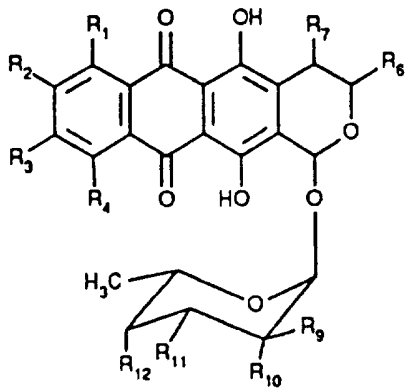


50 (10 , $R_5 = R_8$ = OH)

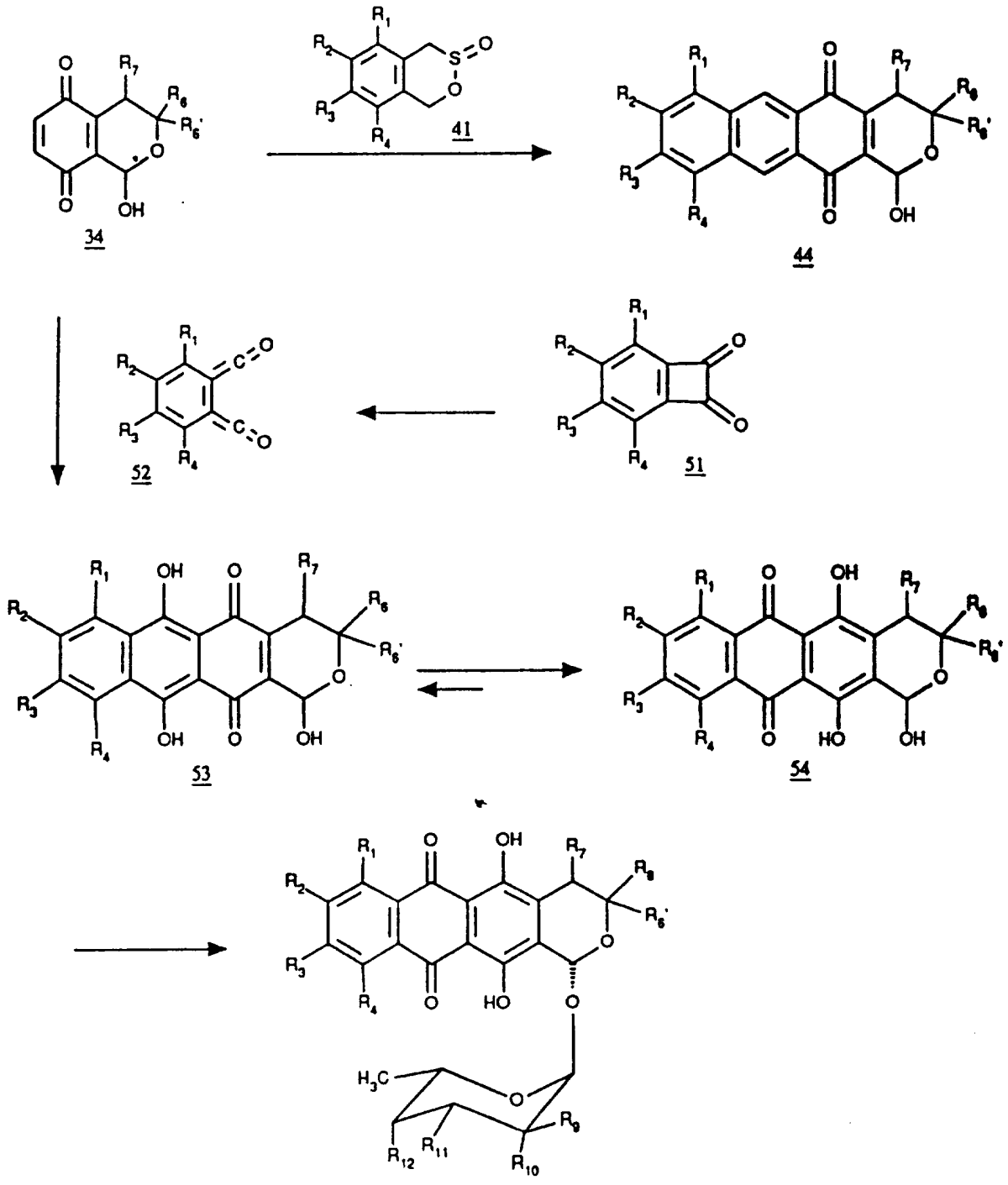


11 (R_6' = H, Y = saccharide, X_3 = 0)

With reference to Reaction Scheme VI, the treatment of pyranoquinone derivatives such as (45), prepared by the method described for the compound (24), with lead tetraacetate in glacial acetic acid can give the acetoxylated pyranoquinones with structures such as (46). These can then be acetylated by treatment with acetic anhydride or acetyl chloride in the presence of a base such as pyridine. The resulting tetracyclic intermediates of formula (47) can be brominated and solvolyzed to give the diacetoxy pyranoquinone aglycone structures (48). Glycosidation can then give the bisacetoxypyranoquinone glycosides of formula (49). These, upon alkaline removal of the acetyl groups, yield glycosides (50) which would exist preferentially in the tautomeric form illustrated as structure (11).

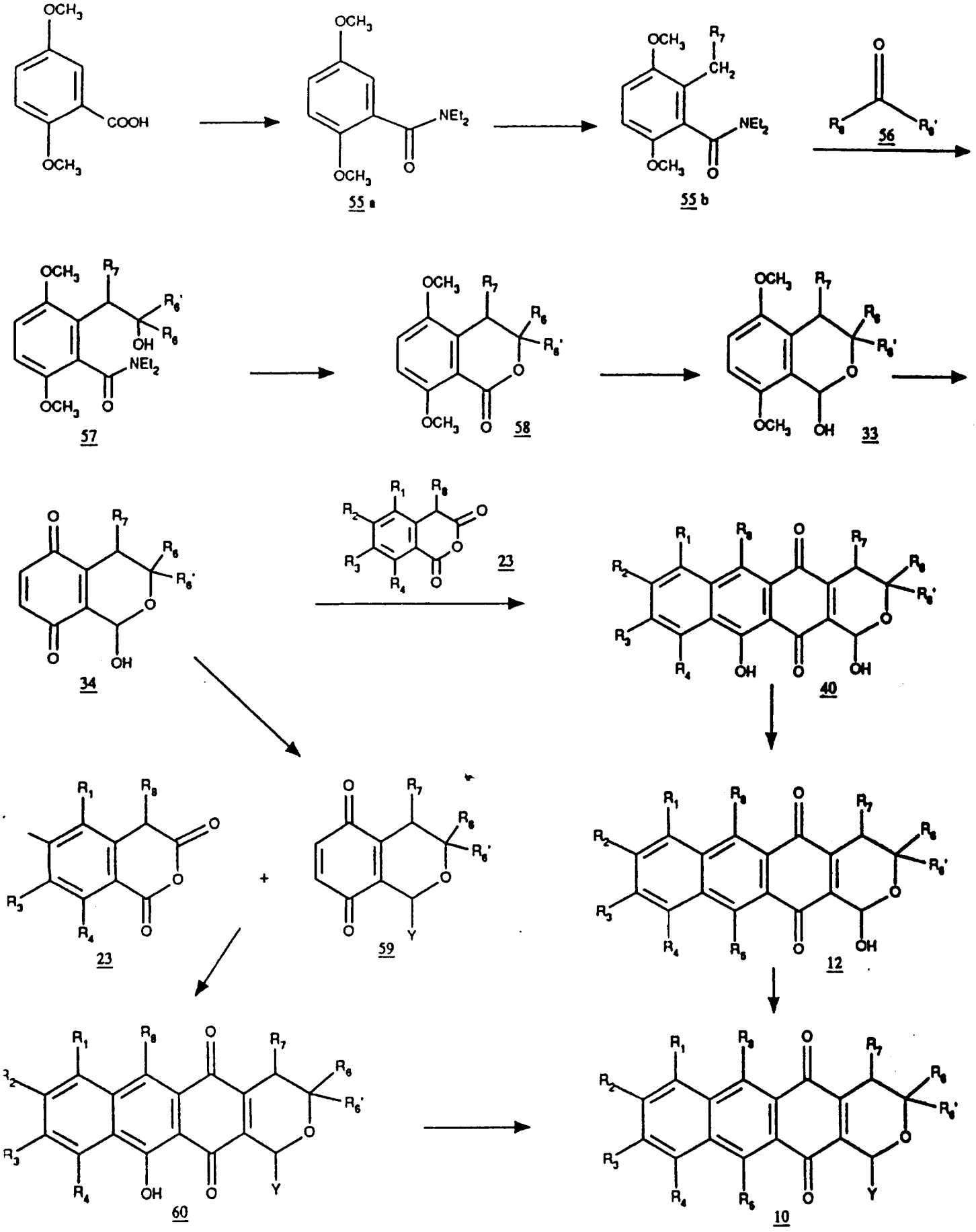
Preferred processes for the preparation of compounds of formula (11) and (44) are illustrated in Reaction Scheme VII. In Reaction Scheme VII pyranoquinones such as (34) can be added to o-quinodimethanes, obtained from the thermolysis of δ-sultine (41), as described in reaction scheme V, to give directly pyranoanthraquinone aglycones of general formula (44). The cycloaddition reaction between a bisbenzoketene derivative such as (52), conveniently generated from benzocyclobutanediones of formula (51) using a method as described by Krohn, [Liebig's Ann. Chem. 943-948 (1988)], can give, in the presence of formula (34) and under ultraviolet irradiation, tetracyclic derivatives such as (53), which will tautomerize to the more favorable structure (54). Glycosidation of aglycones of formula (54) as described in reaction Scheme I can give the glycosides of formula (11).

Reaction Scheme VII



An alternative approach for the preparation of compounds of general formula (12) is shown in scheme **VIII**. With reference to scheme **VIII**, 2,5-dimethoxybenzoic acid is transformed to the benzamide of formula (55a) by first converting the acid, into an acid chloride, with oxalyl chloride in the presence of a base such as pyridine in a solvent such as dichloromethane, and then treating with diethyl amine in ether. The lithio salt of (55a) is then generated with a strong base such as sec-Butyllithium in a convenient solvent such as tetrahydrofuran in the presence of TMEDA and reacted with an electrophile, $L\text{-}CH_2R_7$, wherein R_7 is as defined herein and **L** is a displaceable atom or group such as an halogen. The resulting benzo derivative of formula (55b) is then treated with a strong base such as lithium diisopropyl amide or n-Butyllithium in a solvent such as tetrahydrofuran and added to a carbonyl electrophile of formula (56) to give an adduct of formula (57). The latter can then be cyclised to an isochromanone derivative of formula (58) by treating compound (57) with an acid. Reduction of (58) with a hydride such as DIBAL in a compatible solvent such as dichloromethane can give the 1-hydroxylated isochroman of formula (33). Oxidative demethylation of (33) in a solvent system such as acetonitrile-water with, for example, ceric ammonium nitrate can give an isochromandione such as (34) which can then be transformed to a tetracyclic derivative such as (12) as explained in scheme **IV**. Functional group interconversion of the hydroxyl group of compound (12) into **Y** can be accomplished readily by employing methodology common to one familiar with the art of organic synthesis.

Reaction Scheme VIII

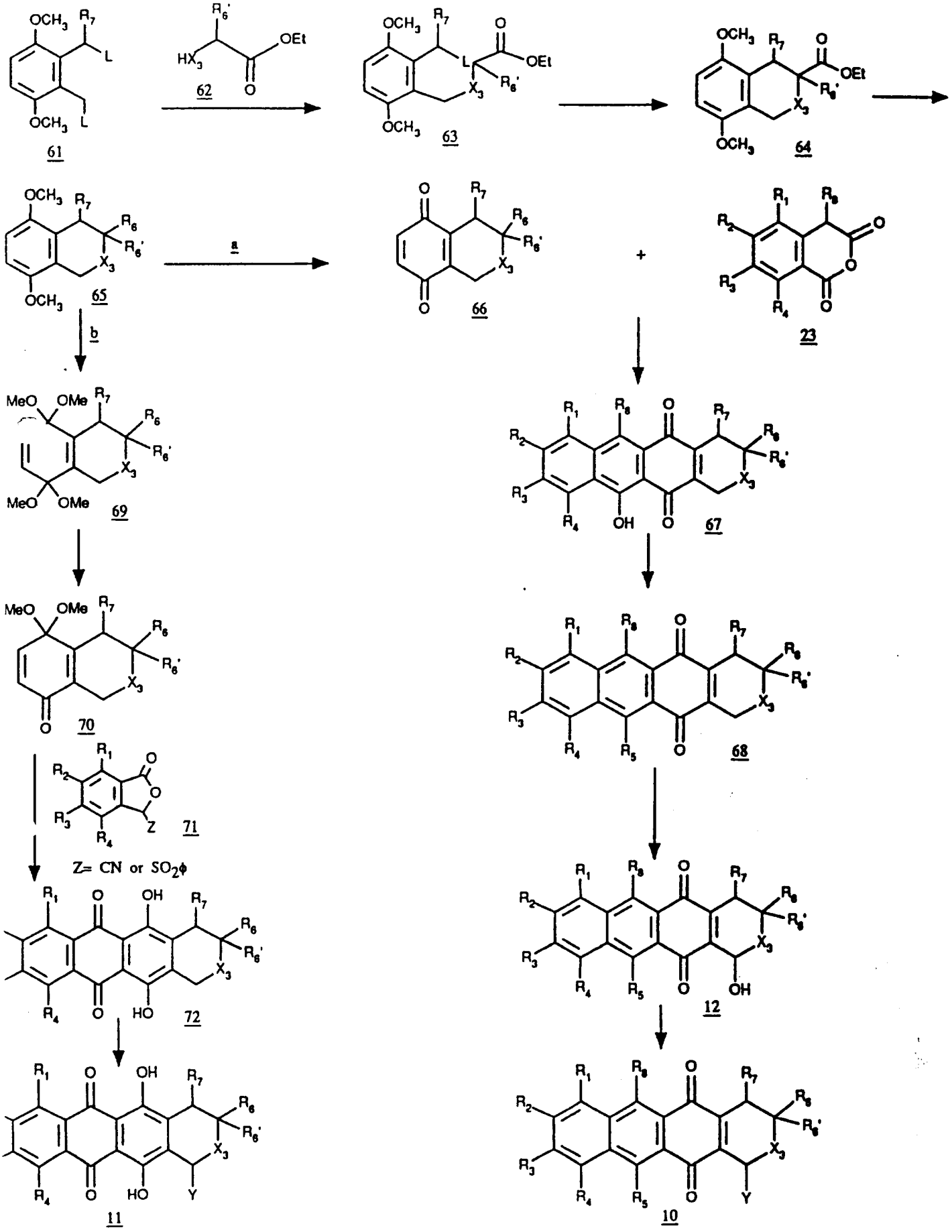


For example, glycosidation as described herein in scheme I of tetracyclic derivative (12) can give structures of formula (10) in which Y is a saccharide; acetylation or benzoylation of compound (12) can give structures of formula (10) in which Y is O-COR and R is an alkyl or aryl; alkylation of the hydroxyl in derivatives of formula (12) can be accomplished with various known electrophiles, for example alkyl halides, orthoformates, or others, with or without catalysis, to give compounds of formula (10) in which Y is an alkoxyl; the hydroxyl group in formula (10) can be converted into a displaceable atom or group L in which L is selected among known leaving groups such as a halide, obtained for example by treating the alcohol with triphenylphosphine in the presence of carbon tetrachloride, carbon tetrabromide or iodine, or a sulfonate such as a mesylate, a tosylate or a triflate, obtained for example by treating the alcohol with mesyl chloride, tosylchloride, triflic anhydride, or the like, in the presence of a base such as pyridine or triethylamine and in an adequate solvent for example benzene or dichlorometane, or L is any other appropriate leaving groups. Displacement of L with various nucleophiles would give compounds of formula (10) with different functional groups Y. For example, Y=CN can be obtained by displacement of L with a cyanide; Y=alkyl, alkenyl, or alkyne, can be obtained by displacement with a carbanion. The above examples are not intended to limit this invention in any way.

In the event that such methodology is not compatible with the other substituents at the R_1,-R_8 positions around the tetracyclic structure (12), then quinone (34) can be transformed into the isochromandione of formula (59), with the desired Y group as defined herein, by applying readily available techniques in organic chemistry. Reaction of an

homophtalic anhydride of formula (23) with an isochroman such as (59) in the presence of a strong base such as lithium diisopropylamide or sodium hydride in a solvent such as tetrahydrofuran can then give the tetracyclic intermediate of formula (60). The phenol of this latter compound can then be transformed into various functional groups by using techniques available to the organic chemists, thus giving the tetracycle of formula (10).

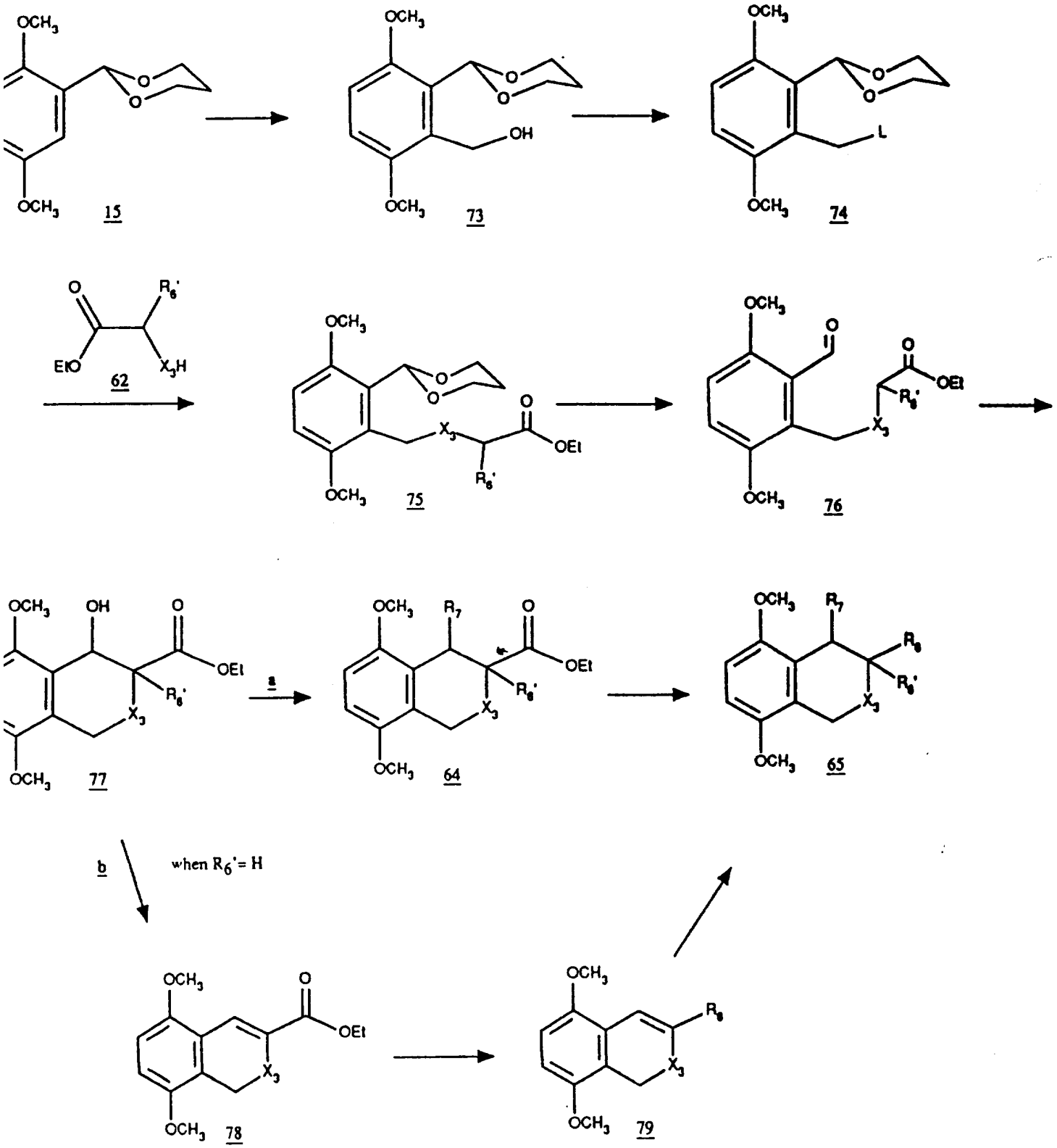
Reaction Scheme IX



A more general approach for the preparation of compounds of general formula (10) is shown in scheme **IX**. With reference to scheme **IX** known compounds of formula (61), in which **L** is a displaceable atom or group such as an halogen or a mesylate, tosylate, or triflate, can be reacted with an intermediate of formula (62) in the presence of base to give an adduct of formula (63). The required acyclic compounds of formula (62) are either known or easily obtainable. Cyclization of (63) to give (64) can be accomplished in an aprotic solvent such as tetrahydrofuran or ether and in the presence of a non nucleophilic base such as sodium hydride or lithium diisopropylamide. The ester group of (64) can then be transformed into various groups, as defined herein for R_6, by using known methodology. Intermediates of general formula (65) can then be used to prepare the desired tetracycle (10) by following route a. Thus oxidative demethylation of (65) with an oxidant such as ceric ammonium nitrate would give quinones of formula (66), which can then be coupled with various homophtalic anhydrides of formula (23) to give tetracyclic heteronaptacenediones of formula (68). Oxidation of (68), for example via free radical bromination with n-bromosuccinamide or bromine in carbon tetrachloride or other compatible solvents, followed by treatment of the bromide with water can lead to aglycones of formula (12). Depending on X_3, alternative oxidation procedures may be required. For example, when X_3=S it is desirable to oxidise the sulfur heteroatom to the sulfoxide (X_3=SO), and then to carry out a Pummeror rearrangement with subsequent hydroxide treatment. Such approaches are common and well described in the literature. The conversion of compound (12) into (10) can be accomplished as described herein in other schemes.

Intermediate (65) can also be used in the direct preparation of the tautomeric form of (10), in the case when R_5=R_8=OH, by following route b. With reference to route b, electrochemical reduction of intermediate (65) in methanol in the presence of sodium methoxide can give the bisketal intermediate of formula (69). Mono deprotection in the presence of a weak acid in aqueous media can give the quinone monoketal of formula (70). This latter intermediate can then be coupled under strongly basic conditions achieved for example with NaH in aprotic media, with known benzofuranones of formula (71) in which Z is an electron withdrawing group such as cyano or phenylsulfone. The resulting heteronaphtacenediones of formula (72) can then be converted to the desired tautomer (11) by using the same methodology as described herein for compounds (25) or (68).

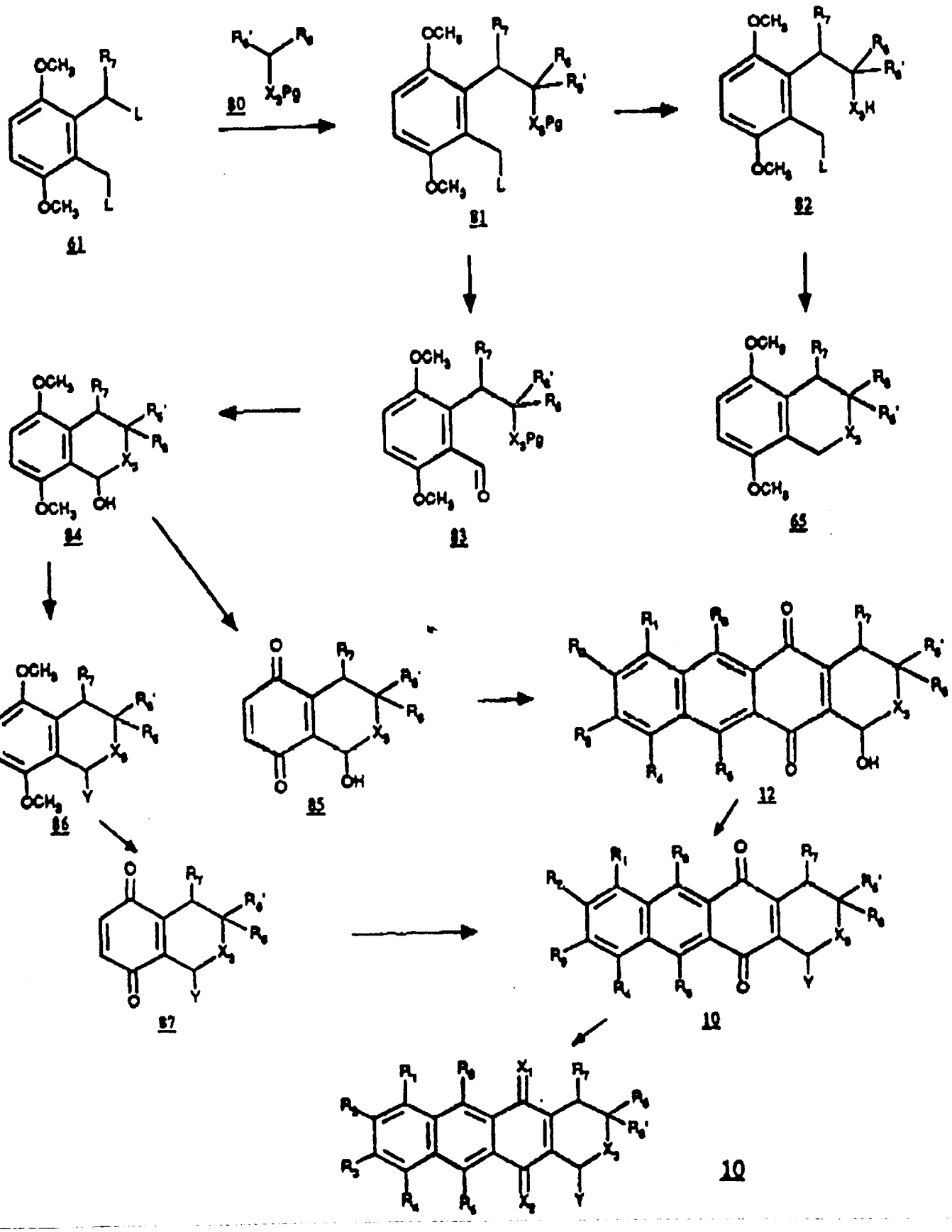
Reaction Scheme X



An alternate method for preparing key bicyclic intermediates of formula (65) is depicted in scheme X. With reference to scheme X, 2,5-dimethoxybenzaldehyde dioxane acetal is treated with a strong base such as n-butyllithium in an aprotic solvent such as diethyl ether, and the resulting lithio salt is alkylated with formaldehyde which can be conveniently generated from p-formaldehyde. The resulting hydroxyl in intermediate (73) can then be converted into a leaving group, for example such as a mesylate, by mesylating with mesyl chloride in the presence of a base such as pyridine in aprotic media. The leaving group of compound (74) can then be displaced with a nucleophile such as (62), as discussed in scheme IX herein, to give key intermediates of formula (75). These latter compounds can then be deprotected in acidic aqueous media to give benzaldehydes of formula (76). Cyclization of these intermediates can be accomplished with bases such as methoxide, carbonates, sodium hydride or lithium diisopropylamides in compatible solvents. Intermediates of formula (77) can then be further transformed to the desired key compounds of formula (65) by following either routes a or b.

In route a, the hydroxyl group of benzoderivative (77) can be transformed into functional groups R_7 to give (64) and subsequently (65), by using simple derivatizing techniques commonly used by the one familiar with organic synthesis. Route b can be employed when R_6' is a hydrogen. In this case, dehydration of (77) to give (78) can be carried out under basic or acidic media. Transformation of the ester functionality of structure (78) into R_6, as defined herein, is possible by using known methods. The resulting derivatives of formula (79) can then be oxidized to give compounds of general formula (65) by using known oxidation techniques.

Reaction Scheme XI

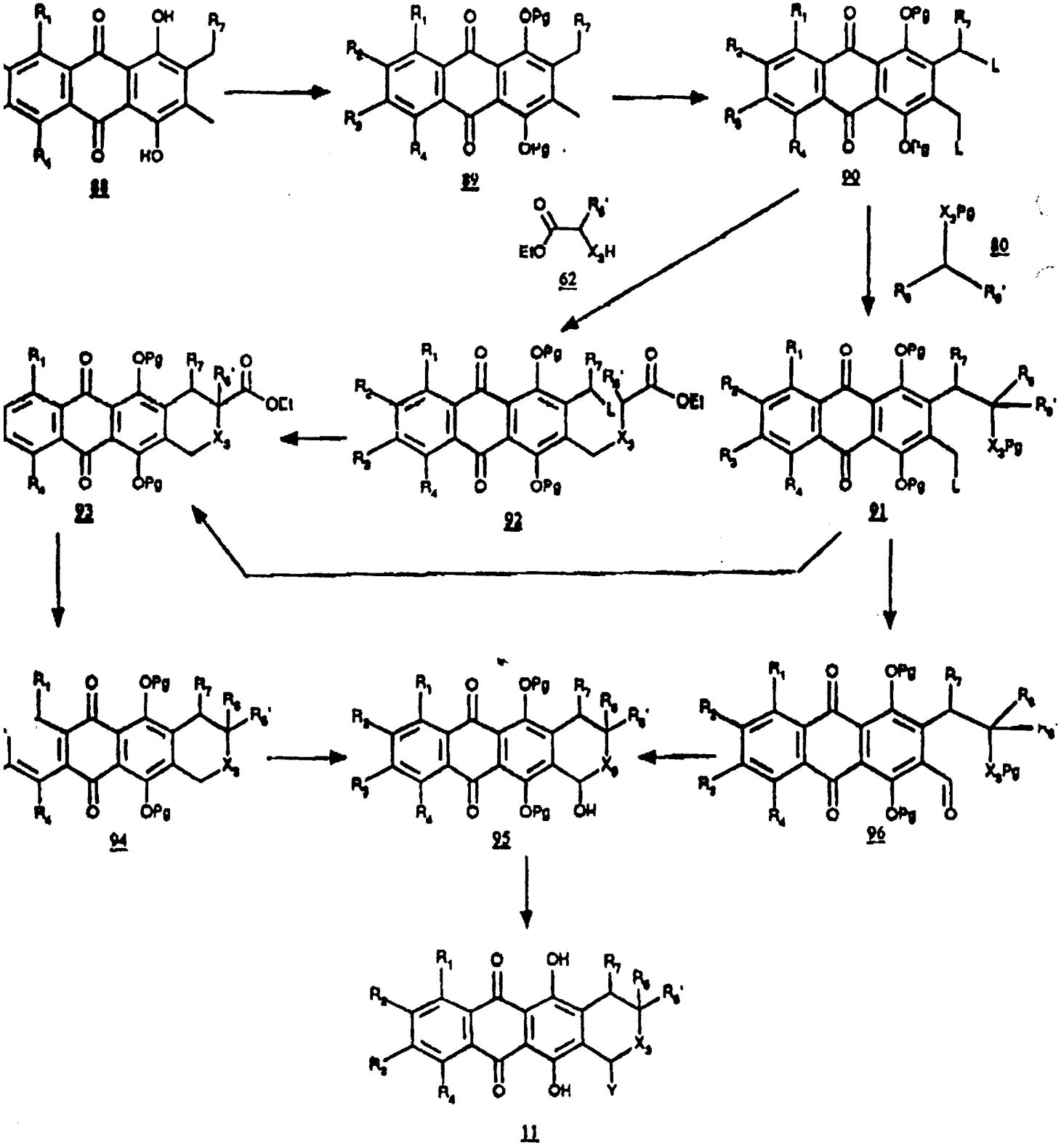


A preferred mode for the preparation of compounds with general structure (10) is shown in scheme **XI**. With reference to scheme **XI**, compounds of formula (61) are coupled, under basic conditions in a suitable solvent such as benzene or tetrahydrofuran, with intermediates of formula (80) to give adducts such as (81). Compounds of formula (80), in which Pg is a protecting group such as benzoyl, and R_6' or R_6 are preferably electron withdrawing groups, are accessible by derivatising known compounds. Deprotection of (81) with sodium hydroxide in protic solvent can give intermediates of formula (82) which can thereafter be cyclized under basic media in aprotic solvent to give the bicyclic intermediates of formula (65).

Although key intermediates such as (65) are readily preparable as described herein, it is best to use compounds of formula (81) for the preparation of quinone derivatives such as (85) or (87). Thus, compounds of formula (81) can be oxidized to give (83) by using known methods. For example, benzylic bromides can be oxidised with sodium bicarbonate in dimethylsulfoxide or with other known reagents to give aromatic aldehydes. Deprotection of (83), for example benzoate hydrolysis with sodium hydroxide, can directly give hydroxylated heterocyclic compounds of formula (84). These latter derivatives are easily oxidatively demethylated with an agent such as ceric ammonium nitrate to give quinones of formula (85). Compounds of formula (10) are readily prepared from (85) by using methodology described herein in other schemes.

Alternatively, functional group interconversion of the hydroxy into **Y** can be accomplished from quinone (85) as described herein in other schemes, or from benzo derivatives (84) to give (86) by employing known techniques. Compounds of formula (10) can then be obtained from (86) by following the same procedure as described for (84).

Reaction Scheme XII



A shorter and more direct approach for the preparation of compounds of general formula (11), which is the tautomer of (10) when R_5=R_8=OH, is shown in scheme XII. With reference to scheme XII a known quinizarin derivative of formula (88) is converted to anthraquinone (90), in which OPg is a protected phenol and L is a displaceable atom or group, by protecting the hydroquinone in (88) as an alkoxyl, an acyl, a silyl or an ether by using known protecting methodology, and then treating for example the resulting protected quinizarin of formula (89) with n-bromosuccinamide or bromine, in a solvent such as carbon tetrachloride under free radical catalysis. The conversion of compound (90) into (11) can be achieved by using methodology already described herein in other schemes. For examples, compound (90) can be converted into (11), via (91), (96) and (95), by using the method as described for the conversion of (61) into (86) in scheme XI; compound (90) can be converted into (93), via (91), by using the method as described for the conversion of (61) into (65) in scheme XI; compound (94) can be obtained from (90), via (92) and (93), by following the sequence as described for converting (61) into (65) in scheme IX. The same methods for transforming (67) into (10) can be used for converting (94) into (11).

It will be appreciated that the anthracyclines of formulae (10) and (11) can be transformed into other structures at the X_1 and X_2 positions using synthetic methods known in the art.

It will be further appreciated that compounds of formula (10) in which X_3=SO or SO_2 can be obtained by oxidizing any of the intermediates in which X_3=S, as convenienced by the synthesis. Convenient reagents for this oxidation are m-chloroperbenzoic acid, hydrogen

peroxide or any other known reagents. Compounds in which X_3=NO can be obtained from those where X_3=NH via oxidation.

It will also be appreciated that the following reactions may require the use of, or conveniently may be applied to, starting materials having protected functional groups, and deprotection might thus be required as an intermediate or final step to yield the desired compound. Protection and deprotection of functional groups may be effected using conventional means. Thus, for example, amino groups may be protected by a group selected from aralkyl (e.g. benzyl), acyl or aryl (e.g. 2,4-dinitrophenyl), subsequent removal of the protecting group being effected when desired by hydrolysis or hydrogenolysis as appropriate using standard conditions. Hydroxyl groups may be protected using any conventional hydroxyl protecting group, for example, as described in "Protective Groups in Organic Chemistry", Ed. J.F.W. McOmie (Plenum Press, 1973) or "Protective Groups in Organic Synthesis" by Theodora W. Greene (John Wiley and Sons, 1981). Examples of suitable hydroxyl protecting groups include groups selected from alkyl (e.g. methyl, t-butyl or methoxymethyl), aralkyl (e.g. benzyl, diphenylmethyl or triphenylmethyl), heterocyclic groups such as tetrahydro-pyranyl, acyl, (e.g. acetyl or benzoyl) and silyl groups such as trialkylsilyl (e.g. t-butyldimethylsilyl). The hydroxyl protecting groups may be removed by conventional techniques. Thus, for example, alkyl, silyl, acyl and heterocyclic groups may be removed by solvolysis, e.g. by hydrolysis under acidic or basic conditions. Aralkyl groups such as triphenylmethyl may be similarly removed by solvolysis, e.g. by hydrolysis under acidic conditions. Aralkyl groups such as benzyl may be cleaved, for example, by treatment with BF_3/etherate and acetic anhydride followed by removal

of acetate groups.

In the above processes, the compounds of formula (10) and (11) are generally obtained as a mixture of diastereoisomers. These isomers may be separated by conventional chromatography or fractional crystallization techniques.

Where the compound of formula (10) or (11) is desired as a single isomer, it may be obtained either by resolution of the final product or by stereospecific synthesis from isomerically pure starting material or any convenient intermediate.

Resolution of the final product, or an intermediate or starting material therefor, may be effected by any suitable method known in the art: see for example, "Stereochemistry of Carbon Compounds", by E.L. Eliel (McGraw Hill, 1962) and "Tables of Resolving Agents", by S.H. Wilen.

The compounds of the formula (10) and (11) possess anti-cancer and anti-tumor activity. The compounds are also believed to possess antibacterial, antifungal and antiviral activity. While it is possible to administer one or more of the compounds of the invention as a raw chemical, it is preferred to administer the active ingredient(s) as a pharmaceutical composition.

In another aspect, the invention therefore provides pharmaceutical compositions primarily suitable for use as antitumor and anticancer agents, comprising an effective amount of at least one compound of the invention or a pharmaceutically acceptable derivative thereof in association with one or more pharmaceutically acceptable carriers and optionally other therapeutic and/or prophylactic ingredients. All the pharmaceutically acceptable salts for example the HCl and tartaric acid salts of the compounds useful as antitumor agents in

mammals, including humans, are included in this invention.

It will be appreciated by those familiar with the art of clinical oncology that the compound(s) of this invention can be used in combination with other therapeutic agents, including chemotherapeutic agents (Cancer: Principles and Practices of Oncology, 3rd Edition, V.T. DeVito Jr., S. Hellman and S.A. Rosenberg; Antineoplastic Agents edited by W.A. Remers, John Wiley and Sons, N.Y., 1984). Thus, it will be understood that the compounds or pharmaceutical compositions of the invention may be formulated with the therapeutic agent to form a composition and administered to the patient or the compounds or compositions and the therapeutic agent may be administered separately, as appropriate for the medical condition being treated.

Therefore, for therapeutic purposes, a compound or composition of this invention can be used in association with one or more of the therapeutic agents belonging to any of the following groups:

1) **Alkylating agents** such as:
   2-haloalkylamines (e.g. melphalan and chlorambucil);
   2-haloalkylsulfides;
   N-alkyl-N-nitrosoureas (e.g. carmustine, lomustine or semustine);
   aryltriazines (e.g. decarbazine);
   mitomycins (e.g. mitomycin C);
   methylhydrazines (e.g. procarbazine);
   bifunctional alkylating agents (e.g. mechlorethamine);
   carbinolamines (e.g. sibiromycin);
   streptozotocins and chlorozotocins;
   phosphoramide mustards (e.g. cyclophosphamide);
   urethane and hydantoin mustards

2) **Antimetabolites** such as:
mercaptopurines (e.g. 6-thioguanine and 6-[methylthio]purine);
azapyrimidines and pyrimidines;
hydroxyureas;
5-fluorouracil;
folic acid antagonists (e.g. amethopterin);
cytarabines;
prednisones;
diglycoaldehydes

3) **Intercalators** such as:
bleomycins and related glycoproteins;
anthracylines (e.g. doxorubicin, daunorubicin, epirubicin, esorubicin, idarubicin, aclacinomycin A);
acridines (e.g. m-AMSA);
hycanthones;
ellipticines (e.g. 9-hydroxyellipticine);
actinomycins (e.g. actinocin);
anthraquinones (e.g. 1,4-bis[(aminoalkyl)-amino]-9,10-anthracenediones);
anthracene derivatives (e.g. pseudourea and bisanthrene);
phleomycins;
aureolic acids (e.g. mithramycin and olivomycin);

4) **Mitotic inhibitors** such as:
dimeric catharanthus alkaloids (e.g. vincristine, vinblastine and vindesine);
colchicine derivatives (e.g. trimethylcolchicinic acid)

epipodophyllotoxins and podophylotoxins (e.g. etoposide and teniposide);
maytansinoids (e.g. maytansine and colubrinol);
terpenes (e.g. helenalin, tripdiolide and taxol);
steroids (e.g. 4β-hyroxywithanolide E);
quassiniods (e.g. bruceantin);
pipobroman;
methylglyoxals (e.g. methylglyoxalbis-(thiosemicarbazone);

5) **Hormones** (e.g. estrogens, androgens, tamoxifen, nafoxidine, progesterone, glucocorticoids, mitotane, prolactin);

6) **Immunostimulants** (e.g. human interferons, levamisole and tilorane);

7) **Monoclonal and polyclonal antibodies;**

8) **Radiosensitizing and radioprotecting compounds** (e.g. metronidazole and misonidazole);

9) **Other miscellaneous cytotoxic agents** such as:
camptothecins;
quinolinequinones (e.g. streptonigrin and isopropylidene azastreptonigrin);
cisplatin and related platinum complexes;
tricothecanes (e.g. trichodermol or vermicarin A);
cephalotoxines (e.g. harringtonine);

10) **Cardioprotecting compounds**, such as (±)-1,2-bis(3,5-dioxopiperazin-1-yl) propane, commonly known as ICRF-187, and ICRF-198;

11) **Drug-resistance reversal compounds** such as P-glycoprotein inhibitors, for example Verapamil;

12) **Cytotoxic cells** such as lymphokine activated killer - cells or T-cells,

13) **Immunostimulants** such as interleukin factors or antigens.

14) **Polynucleotides** of sence or antisencing nature.

15) **Polynucleotides** capable of forming triple helices with DNA or RNA.

16) **Polyethers**

17) **Distamycin and analogs.**

The above list of possible therapeutic agents is not intended to limit this invention in any way.

The pharmaceutical compositions of the invention can be in forms suitable for oral, rectal, nasal, topical (including buccal and sublingual), vaginal or parenteral (including intraarterial intraperitoneal, intramuscular, subcutaneous and intravenous administration) by inhalation or by insufflation. Where appropriate, the formulations may be conveniently presented in discrete dosage units and may be prepared by any method well known in the art of pharmacy. All methods include the step of bringing into

association the active compound with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

For injectable use, the pharmaceutical composition forms include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that easy syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against the contaminating action of microorganisms such as bacteria and fungi. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, polyol (for example, chremophor-el, twin 80, glycerol, dimethyl sulfoxide (DMSO), propylene glycol, and liquid polyethylene glycol, and the like suitable mixtures thereof, and vegetable oils. The proper fluidity can be maintained for example, by the use of a coating such as lecithin, by the maintenance of the required particle size in the case of dispersion and by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active ingredient or ingredients in the

required amount in the appropriate solvent with various of the other ingredients enumerated above, as required followed by filtered sterilization. Generally, dispersions are prepared by incorporating the various sterilized active ingredients into a sterile vehicle which contains the basic dispersion medium and the required other ingredients from those enumerated above. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze-drying technique which yield a powder of the active ingredient plus any additional desired ingredient from a previously sterile-filtered solution thereof.

Pharmaceutical formulations suitable for oral administration may conveniently be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution; as a suspension; or as an emulsion. The active ingredient may also be presented as a bolus, electuary or paste. Tablets and capsules for oral administration may contain conventional excipients such as binding agents, fillers, lubricants, disintegrants, or wetting agents. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils) or preservatives.

As used herein, the expression "pharmaceutically acceptable carrier" includes any and all solvents, dispersion media, coatings, antibacterial and antifungal

agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except isofar as any conventional media or agent is incompatible with the active ingredient, its use in the present compositions is contemplated. Supplementary active ingredients can be incorporated into the inventive compositions.

It is especially advantageous to formulate compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically discrete units suited as unitary dosages for the animal subjects to be treated, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. The specification for the novel dosage unit forms of the invention are dictated by and directly dependent on (a) the unique characteristics of the active material and the particular therapeutic effect to be achieved and (b) the limitations inherent in the art of compounding such an active material for the treatment of disease in living subjects having a diseased condition in which bodily health is impaired as disclosed in detail in this specification.

The dosage of the principal active ingredient for the treatment of the indicated conditions depends upon the age, weight and condition of the subject being treated; the particular condition and its severity; the particular form of the active ingredient, the potency of the active ingredient, and the route of administration. A daily dose of from about 0.001 to about 100 mg/kg of body weight given singly or in divided doses of up to 5 times a day or by

continuous infusion embraces the effective range for the treatment of most conditions for which the novel compounds are effective and substantially non-toxic. For a 75 kg subject, this translates into between about .075 and about 7500 mg/day. If the dosage is divided for example, into three individual dosages, these will range from about .25 to about 2500 mg. of the active ingredient. The preferred range is from about 0.1 to about 50 mg/kg of body weight/day with about 0.2 to about 30 mg/kg of body weight/day being more preferred.

The principal active ingredient is compounded for convenient and effective administration in effective amounts with a suitable pharmaceutically acceptable carrier in dosage unit form as hereinbefore disclosed. A unit dosage form can, for example, contain the principal active ingredient in amounts ranging from about 0.1 to about 1000 mg., with from about 1.0 to about 500 mg. being preferred. Expressed in proportions, the active ingredient is generally present in from about 0.1 to about 500 mg/ml of carrier. In the case of compositions containing supplementary active ingredients, the dosages are determined by reference to the usual dose and manner of administration of the said ingredients.

Antitumor treatment comprises the administration of any of the compounds of this invention in an acceptable pharmaceutical formulation at the effective therapeutic dosage. It is understood that chemotherapy can require the use of any of the compounds of this invention bound to an agent which facilitates targeting the compound to the tumor cells. The agent may be chosen from, for example, monoclonal or polyclonal antibodies, proteins and liposomes. The compounds of this invention could also be administered as monomeric, dimeric or oligomeric metal

chelate complexes with, for example iron, magnesium or calcium.

The compounds of the invention exhibit antitumor or anticancer activity, most notably, antitumor or anticancer activity with human breast cancer, leukemia, colon cancer, lung cancer, renal cancer, ovarian cancer, CNS cancer and melanoma. This list of conditions is however not exclusive, and it is believed that the compounds of the invention will exhibit activity against other tumors and cancers, such as for example pancreatic cancer and bladder cancer.

Certain of the above described intermediates employed in the synthesis of compounds of the invention are also of interest from a pharmacological standpoint. Compounds believed to possess antibacterial, antifungal, antiviral, antitumor and anticancer activity include the following compounds as outlined in the different reaction schemes: (10), (11), as well as the compounds (12), (17), (18), (20), (21), (22), (24), (25), (26), (27), (29), (30), (32) through (41), (43) through (50), (53) and (54), (58), (59), (60), (64) to (70), (72), (77) to (79), (83) to (87), (91) to (96). As with the compounds (10) and (11), the intermediates are preferably administered as a pharmaceutical composition for the treatment of the conditions listed above, and may be administered in the dosages noted above for the compounds (10) and (11). Moreover, the intermediates may be administered as pharmaceutically acceptable salts or as metal chelate complexes where appropriate, and may be administered as a mixture with other of the intermediates compounds, and/or with compounds of the formula (10) or (11), and/or with one or more of the therapeutic agents or agents targeting cancer or tumor cells.

EXAMPLES

The invention will now be further described with reference to the following Examples.

EXAMPLE 1

Step 1: 2,5-Dimethoxybenzaldehydedioxane acetal

A solution containing 200g (1.2 mmol) of 2,5-dimethoxybenzal-dehyde, 150g (2.0 mmol) of 1,3-propanediol, and 1.0g of p-toluene-sulfonic acid in 1.0 L of benzene was refluxed until no more water could be isolated in the Dean-Stark water separator (6 hours). The reaction mixture was then cooled and washed with 400 ml of saturated aqueous sodium bicarbonate, 200 ml of water and 200 ml of saturated aqueous sodium chloride. The organic layer was then dried over $MgSO_4$ and the solvent was removed in vacuo. Distillation of the residue under reduced pressure (B.P. 167°C at 1 mmHg) gave 263.7g (98% yield) of a slightly yellow oil characterised as 2,5-dimethoxybenzaldehydedioxane acetal. ^1H NMR (200 MHz, $CDCl_3$)δ: 1.40 (d m, 1H, HC<u>Ha</u>), 2.24 (m, 1H, HC<u>He</u>), 3.77 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.00 (dt, 2H, O-HC<u>Ha</u>), 4.24 (dd, 2H, O-HC<u>He</u>), 5.84 (s, 1H, O-CH-O), 6.82 (dd, 2H, ArH), 7.19 (d, 1H, ArH).

Step 2: 2,5-Dimethoxy-6-methylbenzaldehyde

To a cooled (-40°C) solution containing 84.0g (0.37 mmol) of 2,5-dimethoxybenzaldehydedioxane acetal in 2.0 L of dry diethyl-ether was added with stirring and under argon 240 ml of a 2.5M n-butyl lithium solution in hexanes. The mixture was stirred for four hours at -25°C and then 24 hours at -10°C. Then to the cooled (-25°C) stirred reaction mixture under argon was added 90.0g of methyl iodide and stirred overnight at room temperature. The solution was then washed twice with 300 ml of water, once with 300 ml of saturated sodium chloride and dried over $MgSO_4$. The organic

solvent was evaporated and the residue was dissolved in 500ml of ether and stirred for 1-1/2 hours with 500 ml of 1N aqueous HCl. The organic layer was separated and washed twice with 200 ml water, once with 200 ml of brine and dried over $MgSO_4$. Evaporation of the solvent gave a yellow oil which was flash chromatographed with 2.5% ethyl acetate in toluene. A 67% yield (45g) of 2,5-dimethoxy-6-methylbenzaldehyde was obtained (MP: 61-61.5°C). ^1H NMR (200 MHz, $CDCl_3$) δ: 2.46 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 6.90 (dd, 2H, ArH), 10.58 (s, 1H, CHO).

Step 3: **5,8-dimethoxy-1-hydroxy-1,3-dihydrobenzo[c] thiophen-2,2-dioxide**

Procedure 1: Under an argon atmosphere, a deoxygenated solution containing 1.60g (8.9 mmol) of 2,5-dimethoxy-6-methyl-benzaldehyde, 11.0g of SO_2 in 100 ml of thiophene free benzene was irradiated at 350 nm for 36 hours. The precipitated crystals (2.01g, 93% yield) were filtered and found sufficiently pure for further use.

Procedure 2: For larger scale, under argon, a deoxygenated solution containing 10.0 g (55.5 mmol) of 2,5-dimethoxy-6-methylbenzaldehyde, 50g of SO_2 in 600 ml of thiophene free benzene was irradiated with a medium pressure mercury immersion lamp with pyrex filtration for four days. The resulting sludge was extracted three times with 400 ml of 1N NaOH and the combined aqueous layer was washed twice with 200 ml of methylene chloride. The aqueous layer was then neutralised with concentrated aqueous HCl and the resulting mixture was then extracted three times with 500 ml of methylene chloride. The combined organic layer was then washed once with 200 ml water, 200 ml of saturated aqueous sodium bicarbonate, 200 ml of water, 200 ml of brine, and then dried over $MgSO_4$. Following evaporation of solvent,

11.2g (83%) of pure 5,8-dimethoxy-1-hydroxy-1,3-dihydrobenzo [c]thiophene-2,2-dioxide was obtained (MP: 140°C decomposes) ^{1}H NMR (200 MHz, $CDCl_3$) δ:3.57 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 4.44 (dd, 2H, CH_2), 5.65 (s, 1H, CH), 6.85 (dd, 2H, ArH).

Step 4: **4,7-dimethoxy-3,8-dihydrobenzo[b]-1,2-oxathiin-2-oxide.**

Following a slightly modified procedure (Charlton J.L., and Durst T., Tet. Lett., 25(46), 5290 - 1984), to a stirred and cooled (0°C) solution of 7.30g (30 mmol) of the 1-hydroxysulfone, prepared in step 3, in 275 ml of methanol was added in portions over fifteen minutes 5.65 g of sodium borohydride. The mixture was stirred for one hour and then warmed at 50°C for five minutes. The reaction mixture was then evaporated to dryness and to the residue was added 200 ml of concentrated aqueous HCl. After warming at 50°C for five minutes, 300 ml of water was added and the aqueous mixture was extracted three times with 300 ml of CH_2Cl_2. The combined organic layer was washed twice with 200 ml of water, once with 200 ml of brine and dried over $MgSO_4$. After evaporation of the solvent, the residue was found to be sufficiently pure to be used in the next step (MP: 90.0-91.0°C). ^{1}H NMR (200 MHz, DMSO-d_6) δ: 3.63 (d, 1H, J=16 Hz, CH_2SO), 3.80 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.13 (d, 1H, J=16 Hz, CH_2SO), 5.14 (dd, 2H, CH_2O-), 6.78 (s, 2H, aryl-H).

Step 5: **Ethyl(5,8-dimethoxyisochroman-3-yl)formate**

In a 250 ml triple necked round bottom flask, equipped with a Dean-Stark, was refluxed a solution containing 30.6g (0.3 mmol) of ethylglyoxalate (Kelly et al, Synthesis, 544, 1972) in 100 ml of benzene until no more water could be separated. A solution containing 4.39g (19.2 mmol) of the sultine from step 4 in 75 ml of benzene was then added

dropwise over 3 hours. During the addition argon was bubbled in the reaction mixture. Reflux was continued overnight and after cooling, the excess glyoxalate was extracted from the mixture with four portions of 200 ml water. The benzene layer was dried and evaporated to give a residue from which was separated 3.13g (61%) of dimethoxyisochroman after flash chromatography from ethyl acetate/toluene. (MP: 59.8°C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.34 (s, 3H, J=7.1 Hz, CH_3), 2.78 (broad dd, 1H, J=17.0, 10.8, 1.3 Hz, HCHaCHC=0), 3.10 (ddd, 1H, J=16.9, 3.9, 1.44 Hz, HCHe, CHC=0), 3.77 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.26 (dd, 1H, J=10.8, 3.9 Hz, OCHC=0), 4.30 (q, 2H, J=7.1 Hz, $-OCH_2$), 4.68 (broad dt, 1H, J=16.0, 1.4, 1.3, ArHCHa0-) 5.07 (broad d, J=16.0 Hz, ArHCHe0-), 6.66 (dd, J=8.9 H, ArH).

Step 6: Ethyl(7-chloro-5,8-dimethoxyisochroman-3-yl)formate

Under argon and at room temperature, was added dropwise 0.820g (7.6 mmol) of t-butylhypochlorite to a stirred solution containing 1.973g (7.4 mmol) of the isochroman from step 5 in 75 ml of anhydrous CH_2Cl_2. The reaction mixture was stirred for 3 hours and then washed successively with 25 ml portions of saturated aqueous sodium thiosulfate, water and brine. After drying over Na_2SO_4, the organic layer was evaporated and the residue was flash chromatographed with 2.5% ethyl acetate in toluene as the eluting solvent mixture. The title compound was obtained in 46% yield (1.02g). (MP: 95.0°C) ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.35 (t, 3H, J=7.1 Hz, CH_3), 2.93 (broad dd, J=16.8, 10.3 Hz, HCHaCHC=0), 3.16 (broad dd, J=16.9, 3.2 Hz, HCHeCHC=0), 3.78 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.27 (dd, J=10.2, 3.3 Hz, -CH), 4.31 (q, 2H, J=7.1Hz, OCH_2), 4.63 (broad d, 1H, J=16.2 Hz, HCHa0), 5.01 (d, 1H, J=16.2 Hz, HCHe0), 6.73 (s, 1H, ArH).

Step 7: **Ethyl(7-chloro-5,8-dioxo-5,8-dihydroiso-chroman-3-yl)formate**

To a stirred solution of 1.0g (3.7 mmol) of the chloroiso-chroman from step 6 in 20 ml of acetonitrile was added dropwise a solution containing 6.25 g (11.4 mmol) of ceric ammonium nitrate in 20 ml of water. The mixture was stirred overnight and then diluted with 50 ml of CH_2Cl_2. The organic layer was separated and the aqueous phase was extracted twice with 25 ml CH_2Cl_2. The combined organic layer was washed once with 50 ml H_2O, 50 ml brine and then dried over Na_2SO_4. After evaporation of solvents, flash chromatography of the residue with a solvent gradient of 5 to 20% ethyl acetate in toluene yielded 495 mg (55%) of the titled compound. (MP: 83.5°C) ^1H NMR (200 MHz, $CDCl_3$) δ: 1.27 (t, 3H, J=7.1 Hz, CH_3), 2.58 (ddt, 1H, J=19.0, 8.8, 3.2 Hz, HCHaCHC=O), 2.83 (d multiplets, 1H, HCHeCHC=O), 4.17 (dd, 1H, J=8.7, 3.3 Hz, OCHC=O), 4.20 (q, 2H, J=7.0 Hz, OCH_2), 4.44 (dt, 1H, J=18.8, 3.4 Hz, HCHaO), 4.78 (d multiplet, 1H, J=18.8, 2.6, 1.7 Hz, HCHeO), 6.95 (s, 1H, C=CH).

Step 8: **Ethyl [11-acetoxy-5,12-dioxo-3,4,5,12-tetrahydro-anthraceno [2,3-c] pyran-3-yl]formate**

To a cooled (0°C) and stirred solution of 203 mg of dry diisopropylamine in 7 ml of dry tetrahydrofuran under argon was added 0.74 ml of a 2.5 M solution of n-butyl lithium in hexanes. The mixture was cooled to -78°C and stirring was continued for 1/2 hour. A solution containing 325 mg (2.0 mmol) of homophthalic anhydride in 7 ml THF was slowly added over five minutes. Next was added in one portion a solution containing 500 mg (1.85 mmol) of the chloroquinone from step 9, in 9 ml THF. The reaction mixture was then stirred for 20 min at -78°C, allowed to warm up to room temperature and stirred for one hour. The reaction was then quenched with 10 ml of saturated ammonium chloride, and partitioned between 10

ml of 5% aqueous HCl and 100 ml CH_2Cl_2. The organic layer was then separated and washed with 25 ml of water, 25 ml of brine and dried over Na_2SO_4. Evaporation of solvents yielded the crude pyranoanthracyclinone which was immediately acetylated in 90 ml of CH_2Cl_2 at room temperature for 10 hours with acetic anhydride (1.25 ml) in the presence of 100 mg of dimethylaminopyridine and 1.5 ml of pyridine. To this reaction mixture was then added 50 g of ice, and the isolated organic layer was washed consecutively with 25 ml portions of 5% aqueous HCl, water and brine. The organic solution was then dried over Na_2SO_4 and evaporated. The residue was then subjected to flash chromatography (5% ethyl-acetate in toluene) and gave 351 mg (34% yield) of the desired titled compound. (MP: 171-173°C) ^{1}H NMR (300 MHz,$CDCl_3$) δ: 1.32 (t, 3H, J=7.1 Hz, CH_3), 2.64 (s, 3H, $COCH_3$), 2.80 (ddt, 1H, J=19.1, 9.0, 3.0 Hz, HC<u>Ha</u>CHC=O), 3.07 (d M, 1H, J=18.9 Hz, HC<u>He</u>CHC=O), 4.29 (dd, 1H, J=9.0, 4.8Hz, OCHC=O), 4.28 (q,1 H, J=7.1 Hz, OCH_2), 4.59 (dt, 1H, J=18.9, 3.2 Hz, HC<u>Ha</u>O), 4.97 (broad d, 1H, J=18.9 Hz, HC<u>He</u>O), 7.72 (m, 2H, ArH), 8.20 (m, 2H, ArH), 8.58 (s, 1H, ArH). CMR (75.44 MHz, $CDCl_3$) δ: 13.9, CH_3, 20.9, CH_3, 24.6, CH_2; 61.6, OCH_2; 71.1, OCH; 123.9, 127.4, 130.3, 130.5, 130.6, aryl CH; 117.9, 128.6, 130.4, 135.6, 140.9, 144.4, 148.2, aryl C; 166.7, 170.4, ester C=O; 181.7, 182.5, quinone C=O. IR (FT, $CDCl_3$) νmax: 1774 acetate C=O, 1750, ester C=O; 1667, 1643, quinone C=O. HRMS calculated for $C_{22}H_{18}O_7$: ($M^{+\cdot}$) 394.1053 found 394.1067.

<u>Step 9:</u> (1S,3S) and (1R,3R)-Ethyl [11-acetoxy-1-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate

A mixture containing 257 mg (0.65 mmol) of the pyranotetra-cycle obtained in step 8, 121 mg of n-bromosuccinimide, and 15 mg of AIBN in 25 ml of carbon tetrachloride was refluxed for 2 hours. After cooling, the solvent was removed <u>in vacuo</u> and the residue was treated with

40 ml of a 1:1 THF/water solvent mixture for one hour. Most of the THF was then removed in a rotaevaporator and the residual aqueous mixture was extracted three times with 30 ml CH_2Cl_2. The combined organic layer was then washed with 25 ml aliquots of water and brine. After drying over Na_2SO_4, the solvent was removed and the residue was flash chromatographed to give 178 mg (67%) of the titled aglycone. (MP: 190-192°C). ^1H NMR (300 MHz, $CDCl_3$) μ235: 1.25 (t, 3H, J=7.1 Hz, CH_3), 2.54 (s, 3H, $OCOCH_3$), 2.59 (dd, 1H, J=11.5, 19.1 Hz, HCHa), 2.89 (dd, 1H, J=4.0, 19.1 Hz, HCHe), 4.21 (q, 2H, J=7.1 Hz, OCH_2), 4.73 (dd, 1H, J=4.1, 11.6 Hz, OCH), 5.89 (bs, 1H, OCH-OH), 7.34 (bs, 1H, exchangeable OH), 7.84 (m, 2H, ArH), 8.25 (m, 1H, ArH), 8.34 (m, 1H, ArH), 8.63 (s, 1H, ArH). CMR (75.44 MHz, DMSO- d_6) δ: 14.0, CH_3; 20.9, CH_2; 61.0, OCH_2; 64.4, OCH; 85.9, O-CH-OH; 120.0, 126.8, 130.8, 130.9, 135.1, aryl CH; 118.0, 128.5, 130.0, 142.1, 142.7, 147.7, aryl C; 169.3,
170.5, ester C=O; 180.8, 183.2, quinone C=O. IR (FT, $CDCl_3$) ^{v}max: 3575, bs, OH; 1774, 1750, ester C=O; 1670, quinone C=O. HRMS calculated for $C_{22}H_{18}O_8$: [M+·] 410.1002 found 410.1010.

Step 10: **(1'S,1R,3S) and (1'S,1S,3R)-Ethyl[11-acetoxy-1-(2',3',6'- trideoxy-3'-trifluoroacetamido-4'-O-p-nitrobenzoyl-L-lyxohexopyranose)-5,12-dioxo-3,4,5,12-tetrahydroanthraceno-(2,3-c) pyran-3-yl] formate**

To a stirred and cooled (-40°C) solution of 222 mg (0.41 mmol) of 2,3,6-trideoxy-3-trifluoroacetamido-1,4-di-O-p-nitrobenzoyl-α (or β)-L-lyxohexopyranose in 20 ml of a 3:1 CH_2Cl_2-Et_2O solvent system was added 0.15 ml of trimethylsilyltrifluoromethane sulfonate under argon atmosphere and in the presence of 4A molecular sieves. The mixture was stirred one hour at -5°C and then cooled to -15°C. A solution containing 121 mg (0.30 mmol) of the pyranoaglycone from step 9 above in 10 ml CH_2Cl_2 was added

next and the mixture was stirred for 20 hours at -15°C. The reaction mixture was then poured in 50 ml of a 1:1 ethyl acetate saturated sodium bicarbonate solvent system, filtered and the separated organic layer was washed with 10 ml of water, 10 ml of brine and dried over Na_2SO_4. After removal of solvents, the residue was flash chromatographed with 10% ethyl acetate in toluene. The desired titled pyranoanthracycline glycosides were obtained as a 1:1 diastereomeric mixture in 65% yield (239 mg). (MP: 160-162°C decomposes). ^1H NMR (200 MHz, $CDCl_3$) of the (1'S, 1S, 3R) diastereomer, δ: 1.24 (d, 3H, J=6.5 Hz, H_3C-6'), 1.37 (t, 3H, J=7.1 Hz, CH_3), 2.06 (m, 2H, H_2C-2'), 2.58 (s, 3H, acetyl, CH_3) 2.74 (dd, 1H, J=17.5, 12 Hz, HCHaCHC=O), 3.17 (dd, 1H, J=19.4, 3.8 Hz, HCHeCHC=O), 4.32 (q, 2H, J=7.0 Hz, OCH_2CH_3), 4.42 (broad q, 1H, J=7.1 Hz, HC-5'), 4.66 (m, 1H, HC-3'), 4.74 (dd, 1H, J=11.9, 3.8 Hz, OCHC=O), 5.47 (broad s, 1H, HC-4'), 5.75 (broad s, 1H, HC-1'), 6.05 (s, 1H, O-CH-O), 6.31 (d, 1H, J=6.6 Hz, NH), 7.76 (m, 2H, ArH), 8.14 (dm, 2H, ArH), 8.31 (dd, 4H, p-nitroben-zoyl-H), 8.60 (s, 1H, ArH). ^1H NMR (200 MHz, $CDCl_3$) of the (1'S, 1R, 3S) diastereomer, δ: 1.26 (d, 3H, J=6.5 Hz, H_3C-6'), 1.35 (t, 3H, J= 7.1 Hz, OCH_2CH_3), 2.06 (m, 2H, H_2C-2'), 2.59 (s, 3H, acetyl- CH_3), 2.76 (dd, 1H, J=18.8, 12 Hz, HCHaCHC=O), 3.15 (dd, 1H, J= 19.4, 4.1 Hz, HCHeCHC=O), 4.31 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.66 (m, 2H, overlaped HC-3' and HC-5'), 4.76 (dd, 1H, J=11.9, 4.0 Hz, OCHC=O), 5.44 (broad s, 1H, HC-4'), 5.65 (broad s, 1H, HC-1'), 6.42 (d, 1H, J=7.4 Hz, NH), 7.76 (m, 2H, ArH), 8.14 (dm, 2H, ArH), 8.32 (dd, 4H, p-nitrobenzoyl -H), 8.60 (s, 1H, ArH). CMR of the mixture (75.44 MHz, $CDCl_3$) δ: 13.9 and 14.0, $CO_2CH_2CH_3$; 16.6, 16.8, 6'-CH_3; 20.9, acyl CH_3; 24.1, 24.6, 2'-CH_2; 29.4, 29.8, 4-CH_2; 45.4, 45.5, CHNH; 61.7, 61.8, ester OCH_2; 65.6, 66.3, 5'-OCH; 66.5, 4'-OCH; 71.8, 72.4, 3-OCH; 87.9, 92.7, 1-O-CH-O; 92.7, 98.0, 1'-O-CH-O; 115.6, quartet, J=289.2 Hz, CF_3; 124.0, 127.57, 127.64, 130.5, 130.6, 130.7, 131.18, 131.22, 135.6, aryl CH; 118.0, 128.4, 134.6, 134.7, 141.0, 141.5, 142.2, 143.1, 148.3, 151.10,

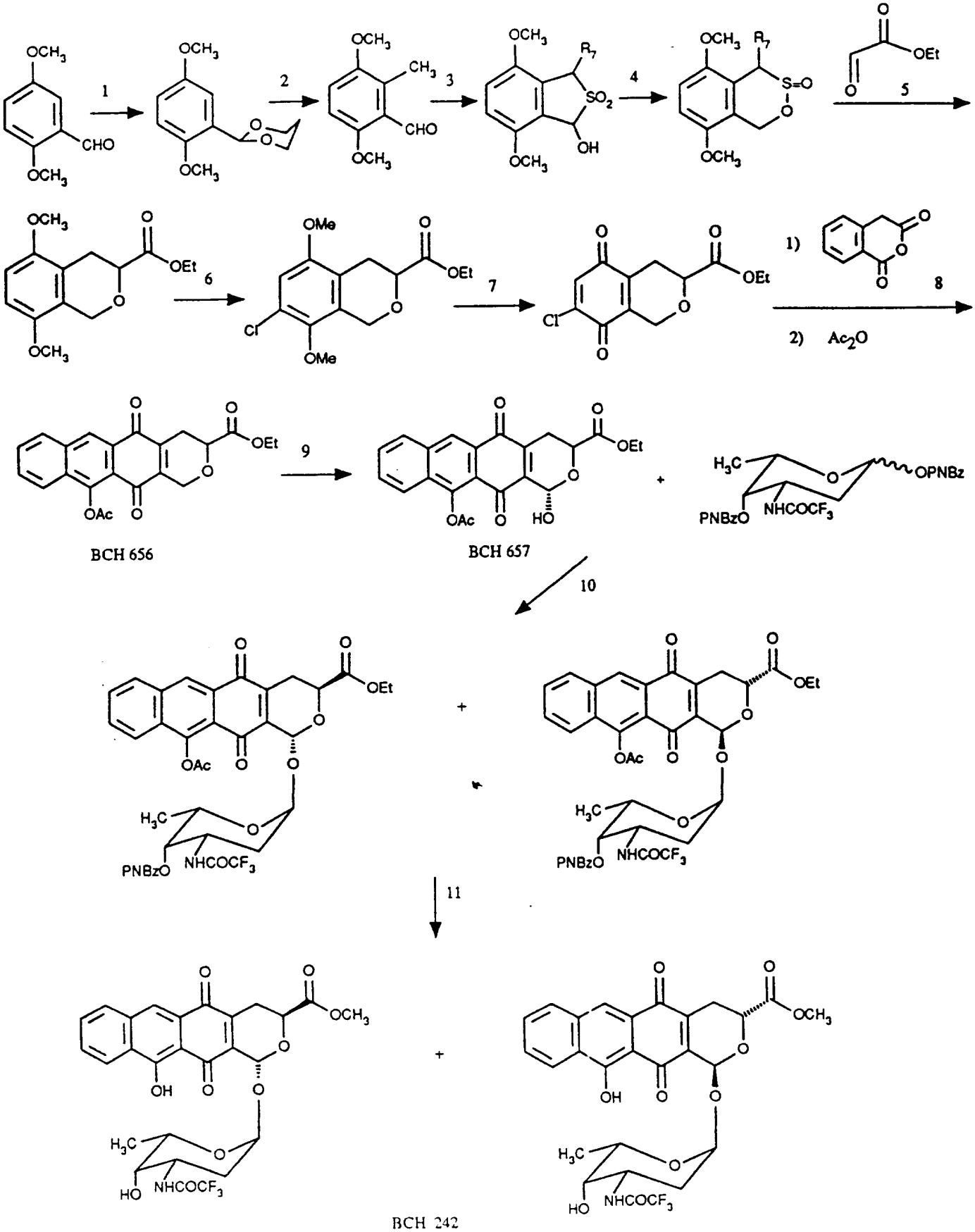
151.14, aryl C; 157.1, quartet, J= 37.7, $\underline{C}OCF_3$; 164.8, 165.2, 169.2, 169.8, 170.2, ester C=O; 181.2, 183.2, quinone C=O. IR (FT, $CDCl_3$) ^{v}max: 1775, 1737, bs, ester C=O; 1670, quinone C=O.

Step 11: (2R,1R,3S) and (1'S,1S,3R)-Methyl[11-hydroxy-1-(2',3,'6'- trideoxy-3'-trifluoroacetamido-L-lyxohexopyranose)-5,12-dioxo-3,4,5,12-tetrahydroanthraceno (2,3-C) pyran-3-yl] formate)

Under argon, at room temperature a solution containing 115 mg (0.13 mmol) of the glycosides from step 10 above in 10 ml of dry methanol was treated with 0.16 ml of a 1.0M $NaOCH_3$ methanolic solution for two hours. The reaction mixture was then quenched with three drops of saturated aqueous NH_4Cl and the solvent was evaporated to dryness. The residue was stirred with pentane for five hours and then filtered. The pentane insoluble portion was then taken up in ether and filtered. The ether was evaporated and the residue was flash chromatographed with a solvent gradient ranging from 50% ethyl acetate in toluene to 20% methanol in ethyl acetate. The titled heteroanthracycline glycosides were obtained in 74% yield (56 mg) as a 1:1 mixture (MP: 147-150°C). ^{1}H NMR (300 MHz, $CDCl_3$) of the (1'S,1R,3S) diastereomer, δ: 1.30 (d, 3H, J=6.9 Hz, H_3C-6'), 1.88 (m, 1H, Hac-2'), 2.04 (m, 1H, HeC-2'), 2.72 (dd, 1H, J=19.0, 12.0 Hz, HC$\underline{Ha}$CHC=O), 3.18 (dd, 1H, J=19.0, 3.9 Hz, HC$\underline{He}$CHC=O), 3.66 (broad s, 1H, HC-3'), 3.86 (s, 3H, OCH_3) 4.33 (m, 2H, HC-4'and HC-5'), 4.73 (dd, 1H, J=11.8, 3.9 Hz, O-CHC=O), 5.50 (broad s, 1H, HC-1'), 5.88 (singlet, 1H, O-CH-O), 6.74 (broad d, 1H, NH), 7.74 (m, 2H, ArH), 7.98 (m, 1H, ArH), 8.18 (s, 1H, ArH), 8.50 (m, 1H, ArH).

^{1}H NMR (300 MHz, $CDCl_3$) of the (1'S,1S,3R) diastereomer, δ: 1.34 (d, 3H, J=7.0 Hz, H_3C-6'), 1.88 (m, 1H, HaC- 2'), 2.04 (m, 1H, HeC-2'), 2.72 (dd, 1H, J=19.0, 12.0 Hz, HC$\underline{Ha}$CHC= O), 3.18 (dd, 1H, J=19.0, 3.9 Hz, HC$\underline{He}$CHC=O), 3.66 (broad s, 1H,

Example 1: Preparation of BCH-242: (1'S, 1R, 3S) and (1'S, 1S, 3R)-Methyl [11-hydroxy-1-(2', 3', 6'-trideoxy-3-trifluroacetamido-L-lyxohexopyranose)-5, 12-dioxo-3, 4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate



BCH 242

HC-3′), 3.87 (s, 3H, OCH_3), 4.33 (m, 1H, HC-4′), 4.59 (broad q, 1H, J=7.1 Hz, HC-5′), 4.73 (dd, 1H, J=11.8, 3.9 Hz, O-CHC-O), 5.60 (broad s, 1H, HC-1′), 6.04 (s, 1H, O-CH-O), 6.74 (broad d, 1H, NH), 7.74 (m, 2H, ArH), 7.98 (m, 1H, ArH), 8.18 (s, 1H, ArH), 8.50 (m, 1H, ArH). HRMS calculated for $C_{28}H_{26}F_3NO_{10}$: [M+] 579.1353, found 579.1358.

EXAMPLE 2

Step 1: **p-Nitrobenzyl(5,8-dimethoxyisochroman-3-yl)formate**

The same methodology as used in Example 1 step 5 was used but with 40g (.18 mmol) of p-nitrobenzylglyoxalate hydrate. A 58% (4.1g) of the titled compound was obtained after flash chromatography (MP: 140-141°C). ^{1}H NMR (200 MHz,$CDCl_3$) δ: 2.84 (dd, 1H, J=16.3, 10.3 Hz,HCHaCHC=O), 3.09 (dd, 1H, J=16.2, 4.0 Hz, HCHeCHC=O), 3.77 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.39 (dd, 1H, J= 10.3, 4.0 Hz, OCHC=O), 4.70 (d, 1H, J=16.0H_3, HCHaO), 5.07 (d, 1H, J=15.9 Hz, HCHeO), 5.36 (broad s, 2H, CH_2), 6.67 (broad s, 2H, ArH), 7.54 (d, 2H, ArH), 8.24 (d, 2H, ArH).

Step 2: **Methyl(5,8-dimethoxyisochroman-3-yl)formate**

To a cooled (0°C) solution containing 500 mg (1.34 mmol) of the p-nitrobenzylate from step 1 in 10 ml THF was added under inert atmosphere 15 ml of a 0.1 M sodium methoxide solution in methanol. After stirring ten minutes, a few drops of saturated aqueous ammonium chloride were added and the solvent was removed. Flash chromatography of the residue gave 282 mg (84%) of the desired isochroman. (MP: 89-90°C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.80 (broad dd, 1H, J=16.9, 10.8 Hz, HCHaCHC=O), 3.12 (ddd, 1H, J=17.0 3.9, 1.4 Hz, HCHeCHC=0, 3.78(s, 3H, OCH_3, 3.81(s, 3H, OCH_3), 3.84 (s, 3H, $COOCH_3$), 4.30 (dd, 1H,

J=10.8, 3.9 Hz, OCHC=O), 4.70 (dt, 1H, J=16.2, 1.5 Hz, HCHaO), 5.08 (d, 1H, J=16.2 Hz, HCHeO), 6.67 (dd, 2H, ArH).

Step 3: Methyl(5,8-dioxo-5,8-dihydroisochroman-3-yl)formate

To a solution containing 265 mg (1.0 mmol) of the isochroman from step 2 in 5 ml of acetonitrile was added dropwise a solution of 1.726g of ceric ammonium nitrate in 5 ml of water at room temperature. After stirring for ten minutes, the mixture was diluted with 50 ml of methylene chloride. The organic phase was separated and the aqueous layer was extracted twice with 25 ml of CH_2Cl_2. The combined organic extract were washed once with water, once with brine and then dried over $MgSO_4$. Evaporation of solvents gave 228 mg (98%) of residue which was found to be above 95% pure pyranoquinone. (MP: 55-58°C) ^1H NMR (200 MHz, $CDCl_3$) δ: 2.68 (dddd, 1H, J=19.0, 9.0, 3.7, 2.8 Hz, HCHaCHC=O), 2.93 (d septet, 1H, J=19.0 Hz, HCHeCHC=O), 3.84 (s, 3H, OCH_3), 4.31 (dd, 1H, J=9.0, 4.4 Hz, CH), 4.52 (dt, 1H, J=18.7, 3.3 Hz, HCHaO), 4.86 (ddd, 1H, J=18.9, 2.8, 1.6 Hz, HCHeO), 6.78 (dd, 2H, HC=CH).

Step 4: Methyl [6-and 11-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl]formate

A solution of 2.5M n-butyl lithium (.20 mmol) is added under argon at 0°C to a stirred solution of 0.07 ml of dry diisopropy-lamine in 2 ml of THF and then stirred for 0.5 hour at -78°C. To the LDA was added dropwise over several minutes a solution of 73 mg (0.45 mmol) of homophthalic anhydride in 2 ml of THF and then 100 mg (0.45 mmol) of the pyranoquinone from step 3 dissolved in 3 ml of THF. The resulting mixture was stirred 20 minutes at -78°C, warmed to room temperature, and stirred for one hour. After quenching with 5 ml of saturated aqueous ammonium chloride the mixture was partitioned between 5 ml of 5% HCl

and 50 ml CH_2Cl_2. The organic layer was separated, washed with 10 ml of brine and dried over Na_2SO_4. Flash chromatography of the residue obtained after evaporation of solvents gave the pyranotetracycles in 54% yield. The less polar regioisomer had (MP: 202-204°C). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.80 (dd t, 1H, J=19.1, 9.1, 3.1 Hz, HCHaCHC=O), 3.11 (dm, 1H, J=19.1 Hz, HCHeCHC=O), 3.84 (s, 3H, OCH_3), 4.35 (dd, J=9.1, 4.3 Hz, OCHC=O), 4.68 (dt, 1H, J=19.0, 3.3 Hz, HCHa-O), 5.06 (broad d, 1H, J=18.9 Hz, HCHe-O), 7.71 (m, 2H, ArH), 7.95 (m, 1H, ArH), 8.13 (s, 1H, ArH), 8.46 (m, 1H, ArH), 13.70 (s, 1H, exchangeable OH). CMR (75.44 MHz, $CDCl_3$), δ: 25.7, CH_2; 53.1, CH_3O; 63.3 CH_2O, 72.2 CHO; 122.7, 125.4, 129.8, 131.1 and 131.9, aryl CH; 127.6, 128.2, 136.4, 143.0 and 143.4 aryl C; 163.1 and 171.0, aryl COH and ester CO; 182.4, 187.1 quinone CO. HRMS calcultaed for $C_{19}H_{15}O_6$ 339.0869 found 339.0853. The more polar regioisomer had (MP: 225-235°C dec.) ^1H NMR (300 MHz, $CDCl_3$) δ 2.85 (ddt, 1H, J=19.0, 9.2 Hz, HCHaCHC=O), 3.13 (dm, 1H, J=19.0 Hz, HCHeCHC=O), 3.86 (s, 1H, OCH_3), 4.37 (dd, J=9.1 et 4.3 Hz, OCHC=O), 4.68 (dt, 1H, J=19.0, 3.4 Hz, HCHa-O), 5.04 (broad d, 1H, J=21.1 Hz, HCHe-O), 7.73 (m, 2H, ArH), 7.97 (m, 1H, ArH), 8.12 (s, 1H, ArH), 8.50 (m, 1H, ArH), 13.85 (s, 1H, exchangeable OH).

Step 5: **Methyl [6-acetoxy-5,12-dioxo-3,4,5,12-tetrahydro-anthraceno [2,3-c] pyran-3-yl]formate**

A mixture containing 60 mg (0.18 mmol) of pyranotetracycle from step 4, 0.25 ml acetic anhydride, 0.3 ml pyridine and 6 mg of dimethylaminopyridine in 20 ml of CH_2Cl_2 was stirred overnight at room temperature under argon atmosphere. The mixture was then diluted with 25 ml CH_2Cl_2 and washed consecutively twice with 15 ml of water, twice with 10 ml of 1N HCl, once with 15 ml of water and dried over $NaSO_4$. Flash chromatography of the residue obtained after flash chromatography yielded 55 mg (81%) of

the titled acetylated pyranotetracycle. (MP: 196-198°C) ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.60 (s, 3H, $COCH_3$), 2.81 (ddt, 1H, J=18.7, 9.1, 3.3 Hz, HCHaCHC=O), 3.10 (dm, 1H, J=19.0 Hz, HCHeCHC=O), 3.85 (s, 3H, OCH_3), 4.31 (dd, 1H, J=9.3, 4.2 Hz, CH), 4.64 (dt, 1H, J=19.0, 3.2 Hz, HCHa-O), 5.02 (broad d, 1H, J=19.0 Hz, HCHe -O, 7.73 (m, 2H, ArH), 8.05 (m, 1H, ArH), 8.13 (m, 1H, ArH), 8.58 (s, 1H, ArH).

Step 6: **(1S, 3S) and (1R, 3R)-Methyl [6-acetoxy-1-hydroxy-5,12- dioxo-3,4,5,12-tetrahydro-anthraceno [2,3-c]pyran-3-yl)formate**

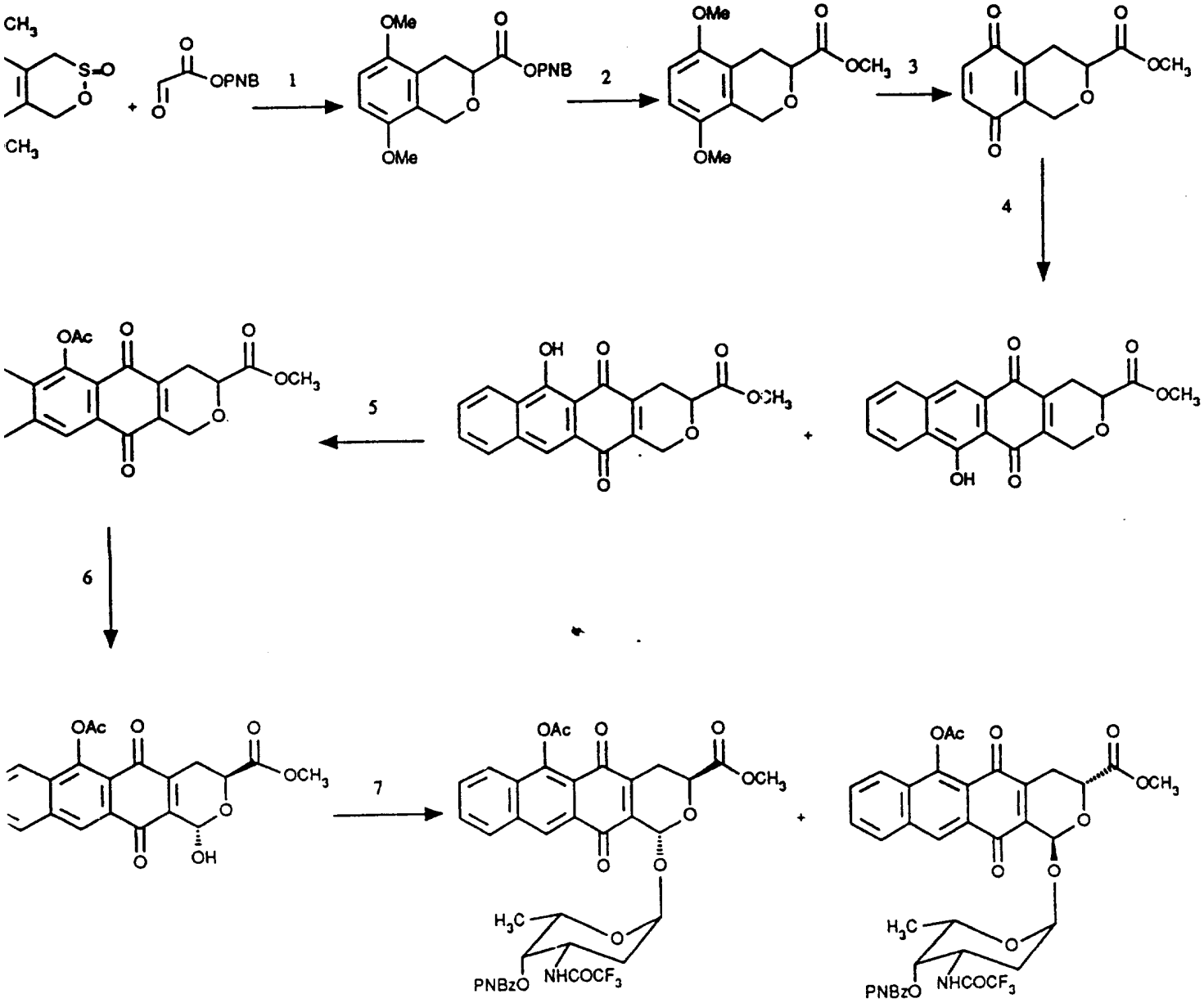
A mixture containing 47 mg (0.12 mmol) of the acetylated pyranotetracycle from step 5, 0.23 mg of N-bromosuccinimide, and 0.1 mg of AIBN in 5 ml of CCl_4 was refluxed for two hours. The solvent was then removed in vacuo and to the residue was added 10 ml of a 3:1 THF-H_2O solvent mixture. After stirring for one hour at room temperature, the mixture was extracted with three 10 ml portions of CH_2Cl_2. The combined organic extracts were washed once with 10 ml of water and dried over Na_2SO_4. Flash chromatography of the residue obtained after removal of solvents gave 35 mg (71%) of the titled pyranotetracyclic aglycone. (MP: 190°C decomposes) ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.60 (dd, 1H, J=19.6, 11.8 Hz, HCHaCHC=O), 3.15 (dd, 1H, J=19.6, 4.3 Hz, HCHeCHC=O), 3.74 (s, 3H, OCH_3), 4.86 (dd, 1H, J=11.5, 4.5 Hz, OCHC=O), 6.21 (d, 1H, J=6.2 Hz, CHOH), 7.34 (d, 1H, J=6.3 Hz, exchangeable OH), 7.75 (m, 2H, ArH), 8.1 (m, 2H, ArH), 8.61 (s, 1H, ArH).

Step 7: **(1'S,1R,3S) and (1'S,1S,3R)-Methyl [6-acetoxy-1-(2', 3',6'-trideoxy-3'-trifluoro-acetamido-4'-O-p-nitrobenzoyl-L-lyxohexopyranose)-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate**

Glycosidation of the pyranoanthraquinone from step 6 could be carried out by the procedure as described for example 1 step 10. The titled pyranoanthraquinone glycoside could be obtained in an overall yield of 77% (MP: 158-160°C of 1'S,1S,3R and 225-227°C of 1'S,1R,3S). ^{1}H NMR (200 MHz, $CDCl_3$,) of the 1'S,1S,3R) diastereomers, δ: 1.25 (d, 3H, J=6.8 Hz,H_3C-6'), 2.06 (m, 2H, H_2C-2'), 2.62 (s, 3H, acetyl CH_3), 2.77 (dd, 1H, J=19.5, 11.3 Hz, HCHaCHC=O), 3.19 (dd, 1H, J=19.3, 3.7 Hz, HCHeCHC=O), 3.89 (s, 3H, OCH_3), 4.42 (broad q, 1H, J=6.9 Hz, HC-5'), 4.65 (m, 1H, HC-3'), 4.78 (dd, 1H, J= 11.4, 3.7 Hz, OCHC=O), 5.48 (broad s, 1H, HC-4'), 5.76 (broad s, 1H, HC-1'), 6.05 (s, 1H, O-CH-O), 6.35 (d, 1H, J=6.4 Hz, NH), 7.76 (m, 2H, ArH) 8.12 (m, 2H, ArH), 8.31 (dd, 4H, p-nitrobenzoyl-H), 8.65 (s, 1H, ArH).

^{1}H NMR (200 MHz, $CDCl_3$) of the (1'S,1R,3S) diastereomer, δ: 1.40 (d, 3H, J=6.6 Hz, H_3C-6'), 2.06 (m, 2H, H_2C-2'), 2.61 (s, 3H, acetyl CH_3), 2.81 (dd, 1H, J=19.0, 11.7, HCHaCHC=O), 3.19 (dd, 1H, J=19.4, 3.9 Hz, HCHeCHC= O,) 3.89 (s, 3H, OCH_3), 4.72 (broad m, 3H, overlaped HC-5', HC-3', OCHC=O), 5.46 (broad s, 1H, HC-4'), 5.67 (broad s, 1H, HC-1'), 6.26 (s, 1H, O-CH-O), 6.41 (d, 1H, J=8.0 Hz, NH), 7.72 (m, 2H, ArH), 8.18 (dm, 2H, ArH), 8.35 (dd, 4H, p-nitrobenzoyl-H), 8.67 (s, 1H, ArH).

Example 2: Preparation of (1'S, 1R, 3S) and (1'S, 1S, 3R)-Methyl [6-acetoxy-1-(2', 3', 6'-trideoxy-3'-trifluoroacetamido-4'-O-p-nitrobenzoyl-L-lyxohexopyranose)-5,12-dioxo-3, 4, 5, 12-tetra-hydroanthraceno [2,3-c] pyran-3-yl] formate



EXAMPLE 3

Step 1: **Ethyl(6 and 11 hydroxy-5,12-dioxo-3,4,5,12-tetrahydro-anthraceno[2,3-c]pyran-3-yl)] formate**

A solution of 2.5M n-butyl lithium (.20 mmol) was added under argon at 0°C to a stirred solution of 0.07 ml of dry diisopropylamine in 2 ml of THF and stirred for 0.5 hour at -78°C. To the LDA was added dropwise over several minutes a solution of 73 mg (0.45 mmol) of homophtalic anhydride in 2ml of THF and then 100 mg (0.45 mmol) of the pyranoquinone, from the previous step, dissolved in 3 ml of THF. The resulting mixture was stirred 20 minutes at -78°C, warmed to room temperature, and stirred for one hour. After quenching with 5 ml of saturated aqueous ammonium chloride the mixture was partitioned between 5 ml of 5% HCl and 50 ml CH_2Cl_2. The organic layer was separated, washed with 10 ml of brine and dried over Na_2SO_4. Flash chromatography of the residue (10% EtOAc in toluene) obtained after evaporation of solvents, gave a polar component which was tentatively assigned as the 6-hydroxytetracycle, in 15% yield. (MP: 150-152°C.). ^1H NMR (200 MHz, $CDCl_3$) δ: 1.36 (t, 3H, J=7.1 Hz, CH_3), 2.84 (ddt, 1H, J=19.1, 9.1, 3.2 Hz, HCHaCHC=O), 3.13 (d m, 1H, J=19.1 Hz, HCHeCHC=O), 4.32 (q, 2H, J=7.1 Hz, OCH_2), 4.34 (dd, J=9.1, 4.3 Hz, OCHC=O), 4.67 (dt, 1H, J=19.0, 3.3 Hz, HCHa-O), 5.06 (broad d, 1H, J=19.0 Hz, HCHe-O), 7.71 (multiplet, 2H, ArH), 7.94 (multiplet, 1H, ArH), 8.11 (s, 1H, ArH), 8.47 (multiplet, 1H, ArH), 13.7 (s, 1H, exchangeable OH). CMR (75.44 MHz, $CDCl_3$) δ: 14.0, CH_3; 24.4, CH_2; 61.6, 63.2, OCH_2; 71.7, OCH; 121.9, 125.0, 129.4, 130.7, 131.5, aryl CH; 127.2, 127.6, 131.0, 136.0, 141.7, 144.2, 162.7, aryl C; 170.4, ester C=O; 183.5, 187.5, quinone C=O. IR (FT, $CDCl_3$) νmax: 3405, bs, OH; 1748, ester C=O; 1660, 1644, quinone C=O, 1609, C=C. HRMS calculated for $C_{20}H_{16}O_6$: [M+·]= 352.0947 found 352.0997.

The less polar component, tentatively assigned as ethyl [11- hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno (2,3-C) pyran- 3-yl] formate, was obtained in 32% yield. (MP: 149-150°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.35 (t, 3H, J=7.1 Hz, CH_3), 2.78 (ddt, 1H, J=3.4, 9.1, 19.0 Hz, HCHa), 3.07 (d m, 1H, J=19.0 Hz, HCHe), 4.31 (overlaped of with dd, 3H, OCH_2 and OCH), 4.65 (dt, 1H, J=3.3, 18.8 Hz, HCHa) 5.04 (bd, 1H, J=18.8 Hz, HCHe), 7.71 (m, 2H, ArH), 7.93 (dd, 1H, J=1.3, 7.3 Hz, ArH), 8.07 (s, 1H, ArH), 8.43 (dd, 1H, J=1.2, 7.2 Hz, ArH). CMR (75.44 MHz, $CDCl_3$) δ: 13.9, CH_3; 24.8, CH_2; 61.6, 62.6, OCH_2; 71.6, OCH; 122.1, 124.8, 129.3, 130.6, 131.4, aryl CH; 106.1, 127.0, 127.6, 135.7, 142.6, 143.0, 162.6, CH; 170.3, ester C=O; 182.0, 186.0, quinone C=O. IR (FT, $CDCl_3$) νmax: 3590, broad, OH; 1748, ester C=O; 1662, 1645, quinone C=O, 1607, C=C. HRMS calculated for $C_{20}H_{16}O_6$: [M+·]=352.0947 found 352.0946. In addition, ethyl (5,12-dihydroxy-6,11-dioxo-3,4,6,11-tetrahy-droanthraceno [2,3-c] pyran-3-yl)formate BCH-650, could be isolated in 10% yield. (MP: 153-154°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.36 (t, 3H, J=6.0 Hz, CH_3), 2.96 (ddt, 1H, J=2.0, 10.1, 18.2 Hz, HCHa), 3.26 (ddd, 1H, J=1.8, 4.0, 18.3 Hz, HCHe), 4.33 (q, 2H, J=6.2 Hz, OCH_2), 4.37 (dd, 1H, J=4.0, 10.0 Hz, OCH), 4.82 (dt, 1H, J=2.0, 17.6 Hz, O-HCHa), 5.23 (d, 1H, J=17.5 Hz, O-HCHe), 7.85 (m, 2H, ArH), 8.35 (m, 2H, ArH), 13.17 (s, 1H, ArOH), 13.34 (s, 1H, ArOH).

Step 2: Ethyl [6-acetoxy-5,12-dioxo-3,4,5,12-tetrahydroan-
thraceno (2,3-c) pyran-3-yl] formate

A mixture containing 60 mg (0.18 mmol) of the more polar pyranotetracycle, from the previous step, 0.25 ml acetic anhydride, 0.3 ml pyridine and 6 mg of dimethylaminopyridine in 20 ml of CH_2Cl_2 was stirred overnight at room temperature under argon atmosphere. The

mixture was then diluted with 25 ml CH_2Cl_2 and washed consecutively twice with 15 ml of water, twice with 10 ml of 1N HCl, once with 15 ml of water and dried over $NaSO_4$. Flash chromatography of the residue obtained after flash chromatography yielded 55 mg (81%) of the titled acetylated pyranotetracycle. (MP: 196-198°C). ^1H NMR (300 MHz, $CDCl_3$), δ: 1.34 (t, 3H, J=7.2 Hz, CH_3), 2.63 (s, 3H, $COCH_3$), 2.78 (ddt, 1H, J=3.3, 9.1, 18.7 Hz, HCHa), 3.10 (dm, 1H, J=19.0 Hz, HCHe), 4.29 (q, 2H, J=7.2 Hz, OCH_2), 4.31 (dd, 1H, J=4.2, 9.3 Hz, OCH), 4.61 (dt, 1H, J=3.2, 19.0 Hz, HCHa-O), 5.02 (bd, 1H, J=19.0 Hz, HCHe-O), 7.73 (m, 2H, ArH), 8.05 (m, 1H, ArH), 8.13 (m, 1H, ArH), 8.58 (s, 1H, ArH). IR (FT,$CDCl_3$) νmax: 1773, 1751, ester C=0; 1667, 1644, quinone C=0; 1618, C=C. HRMS calculated for $C_{22}H_{18}O_7$: [M+] 394.1053 found 394.1020.

Step 3: **(1S,3S) and (1R,3R)-Ethyl-[6-acetoxy-1-hydroxy-5,12- dioxo-3,4,5,12-tetrahydroanthraceno (2,3-c) pyran-3-yl] formate**

A mixture containing 47 mg (0.12 mmol) of the acetylated pyranotetracycle 0.23 mg of N-bromosuccinimide, and 0.1 mg of AIBN in 5 ml of CCl_4 was refluxed for two hours. The solvent was then removed in vacuo and to the residue was added 10 ml of a 3:1 THF-H_2O solvent mixture. After stirring for one hour at room temperature, the mixture was extracted with three 10 ml portions of CH_2Cl_2. The combined organic extracts were washed once with 10 ml of water and dried over Na_2SO_4. Flash chromatography of the residue obtained after removal of solvents gave 35 mg (71%) of pyranotetracyclic aglycone (MP: 215-220°C decomposes). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.35 (t, 3H, J=7.1 Hz, CH_3), 2.61 (s, 3H, $OCOCH_3$) 2.71 (dd, 1H, J=19.6, 11.8 Hz, HCHaCHC= O), 3.15 (dd, 1H, J=19.6, 4.3 Hz, HCHeCHC=O), 4.32 (q, 2H, J=7.1 Hz, OCH_2), 4.86 (dd, 1H, J=11.5, 4.5 Hz, OCHC=O), 6.22 (s, 1H, CHOH), 7.74 (m, 2H, ArH), 8.12 (m,

2H, ArH), 8.61 (s, 1H, ArH). CMR (75.44 MHz, DMSO-d_6) δ: 13.9, CH_3; 20.9, CH_3; 24.7, CH_2; 60.9, OCH_2; 64.6, OCH; 85.9, O-CH-O; 124.1, 126.7, 130.8, 130.9, 131.0, aryl CH; 118.1, 126.6, 129.7, 135.3, 141.1, 143.9, 147.6, aryl C; 169.3, 170.5, ester C=O; 181.3, 182.6, quinone C=O. IR (FT, $CDCl_3$) νmax: 3365, bs, OH; 1774, 1748, ester C=O; 1668, quinone C=O. HRMS calculated for $C_{22}H_{18}O_8$: [M+·] 410.1002 found 410.1009.

Step 4: **(1'S,1R,3S) and (1'S,1S,3R)-Ethyl [6-acetoxy-1-(2',3', 6'-trideoxy-3'-trifluoroacetamido-4'-O-p-nitrobenzoyl-L-lyxohexopyranose)-5,12-dioxo-3,4,5,12-tetrahydroan-thraceno (2,3-c) pyran-3-yl] formate**

Glycosidation of the pyranoanthraquinone from step 3 above, could be carried out by following the procedure as described in example 1, step 10. The titled pyranoanthraquinone glycoside could be obtained in an overall yield of 77% (MP: 158-160°C of 1'S,1S,3R and 225-227°C of 1'S,1R,3S). ^{1}H NMR (300 MHz, $CDCl_3$) of the (1'S,1S,3R) diastereomers, δ: 1.25 (d, 3H, J=6.8 Hz, H_3C-6'), 1.36 (t, 3H, J=7.0 Hz, CH_3), 2.06 (m, 2H, H_2C-2'), 2.62 (s, 3H, acetyl, CH_3), 2.77 (dd, 1H, J=19.5, 11.3 Hz, HCHaCHC=O), 3.19 (dd, 1H, J=19.3, 3.7 Hz, HCHeCHC= O), 4.31 (q, 2H, J-7.0 Hz, OCH_2), 4.42 (broad q, 1H, J=6.9 Hz, HC-5'), 4.65 (m, 1H, HC-3'), 4.78 (dd, 1H, J=11.4, 3.7 Hz, OCHC=O), 5.48 (broad s, 1H, HC-4'), 5.76 (broad s, 1H, HC-1'), 6.05 (s, 1H, O-CH-O), 6.35 (d, 1H, J=6.4 Hz, NH), 7.76 (m, 2H, ArH) 8.12 (m, 2H, ArH), 8.31 (dd, 4H, p-nitrobenzoyl-H), 8.65 (s, 1H, ArH). ^{1}H NMR (300 MHz, $CDCl_3$) of the (1'S,1R,3S) diastereomer, δ: 1.40 (d, 3H, J=6.6 Hz,H_3C-6'), 1.37 (t, 3H, J= 7.0 Hz, CH_3), 2.06 (m, 2H, H_2C-2'), 2.61 (s, 3H, acetyl, CH_3), 2.81 (dd, 1H, J=19.0, 11.7, HcHaCHC=O), 3.19 (dd, 1H, J=19.4, 3.9 Hz, HCHeCHC=O), 4.31 (q, 2H, J=7.0 Hz, OCH_2), 4.72 (broad m, 3H, overlaped HC-

5′, HC-3′, OCHC=O), 5.46 (broad s, 1H, HC-4′), 5.67 (broad s, 1H, HC-1′), 6.26 (s, 1H, O-CH-O), 6.41 (d, 1H, J=8.0 Hz, NH), 7.72 (m, 2H, ArH), 8.18 (dm, 2H, ArH), 8.35 (dd, 4H, p-nitrobenzoyl-H), 8.67 (s, 1H, ArH). CMR of the diastereomeric mixture (75.44 MHz, $CDCl_3$) δ: 14.3 and 14.5, $CO_2CH_2\underline{C}H_3$; 17.0 and 17.2, 6′-CH_3; 21.4, acyl CH_3; 24.9 and 25.4, 2′-CH_2; 29.9 and 30.0, 4-CH_2; 45.9 and 46.0, CHNH; 62.1 and 62.2, ester OCH_2; 66.2 and 66.8, 5′-OCH; 66.9 and 67.1, 4′-OCH; 72.2 and 72.8, 3-OCH; 88.0 and 92.7, 1-O-CH-O; 92.8 and 98.7, 1′-O-CH-O; 113.1, quartet, J=287.1 Hz, CF_3; aromatic CH: 124.5, 127.8, 128.1, 131.0, 131.2, 131.6, 131.7, 135.0, aromatic quaternary C: 118.5, 128.9, 130.9, 131.0, 131.2, 134.97, 138.16, 138.23, 139.5, 140.0, 144.9, 145.8, 148.85, 148.94, 151.7, 157.5, quartet J=37.3 Hz, $\underline{C}OCF_3$; 165.4, 165.7, 169.6, 169.7, 170.1, 170.5, ester C=O; 182.0, 182.3, 182.7, quinone C=O. IR (FT, $CDCl_3$) νmax: 1774, 1737, broad, ester C=O; 1669, quinone C=O, 1532, amide.

<u>Step 5:</u> Ethyl [6-11-hydroxy-5,12-tetrahydroanthraceno(2,3-c) pyran-3-yl]formate and Ethyl [11-acetoxy-6-hydroxy-5, 12-dioxo-3,4,5,12-tetrahydroanthraceno(2,3-c)pyran-3-yl]formate

A mixture containing 387 mg (1.1 mmol) of the unacetylated pyranotetracycle obtained in step 1 above, 2.5g lead tetraacetate, 60 ml of acetic acid, and 30 ml of CH_2Cl_2 was stirred for 48 hours under argon at room temperature. The mixture was then diluted with 100 ml of CH_2Cl_2, extracted twice with 50 ml of water and dried over Na_2SO_4. After removal of solvents, the residue was found to contain the titled compounds. CMR (75.44 MHz, $CDCl_3$) δ: 13.94, 20.66, 20.80, 24.98, 25.68, 61.57, 61.70, 63.60, 63.67, 71.97, 72.07, 126.76, 126.82, 127.48, 127.53, 134.19, 135.04, 135.07, 157.10, 159.03, 170.46, 170.52, 181.37, 188.78, 188.82, FT (IR, $CDCl_3$), νmax: 1759.8,

1754.5, ester C=O; 1671.7, 1634.7, quinone C=O.

Step 6: Ethyl [6,11-diacetoxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno (2,3-c) pyran-3-yl] formate

The residue from step 5 above was added to a solution containing 5 ml of acetic anhydride, 6 ml of pyridine and 60 mg of dimethylaminopyridine in 50 ml of CH_2Cl_2. The mixture was stirred at room temperature overnight under argon and then added to 50g of ice. The aqueous layer was separated and extracted twice with 50 ml of CH_2Cl_2. The combined organic extracts were then consecutively washed once with 25 ml of water, twice with 25 ml of IN HCl, 25 ml of water, 25 ml of brine and then dried over Na_2SO_4. After evaporation of solvents, flash chromatography of the residue yielded 175 mg (35%) of the titled bisacetylated pyranoanthraquinone. (MP: 203-205°C). ^1H NMR (200 MHz, $CDCl_3$) δ: 1.36 (t, 3H, J=7.1 Hz, CH_3), 2.50 (s, 3H, $COCH_3$), 2.54 (s, 3H, $COCH_3$), 3.05 (broad m, 2H, $C\underline{H}_2CHC=O$, 4.35 (masked dd, 1H, OCHC=O), 4.32 (q, 2H, J=7.1 Hz, $OC\underline{H}_2CH_3$), 4.75 (broad d, 1H, J=16.7 Hz, $HC\underline{Ha}$-O), 5.11 (broad d, 1H, J=16.5 Hz, $HC\underline{He}$-O), 7.75 (m, 2H, ArH), 8.16 (m, 2H, ArH). IR (FT, $CDCl_3$) ^{v}max: 1771, broad s, ester CO; 1677, quinone C=O, 1591, C=C. HRMS calculated for $C_{24}H_{19}O_{10}$: 451.1029 found 451.1061.

Step 7: (1S,3S) and (1R,3R) Ethyl [11-acetoxy-1,6-dihydroxy- 5, 12-dioxo-3,4,5,12-tetrahydroanthraceno (2,3-c) pyran- 3-yl] formate.

A mixture containing 75 mg (0.17 mmol) of the pyranotetracy- cle from step 6 above, 32 mg (0.17 mmol) of n-bromosuccinimide, 1 mg AIBN in 15 ml of CCl_4 was refluxed under argon for 2.5 hours. After removal of solvent, 25 ml

of a 4:1 THF-H_2O solvent mixture was added to the residue and stirred for 0.5 hour. The mixture was then extracted three times with 25 ml of CH_2Cl_2 and the combined extracts were washed with 25 ml of water, 25 ml of brine and dried over Na_2SO_4. After evaporation of solvent, flash chromatography of the residue gave 61 mg (77%) of the desired bis acetylated tetracyclic aglycone. (MP: 220-250°C decomposes). ^1H NMR (300 MHz, DMSO-d_6) δ: 1.25 (t, 3H, J=7.1 Hz, CH_3), 2.42 (s, 3H, $COCH_3$), 2.35 (bm, 1H, HCHa), 2.47 (bm, 1H, HCHe), 4.21 (q, 2H, J=7.1 Hz, OCH_2), 4.42 (m, 1H, OCH), 6.11 (d, 1H, J= 5.8 Hz, O-CH-OH), 7.42 (d, 1H, J=5.8 Hz, exchangeable, OH), 7.95 (m, 2H, ArH), 8.12 (m, 1H, ArH), 8.22 (m, 1H, ArH), 13.3 (s, 1H, exchangeable, ArOH). IR (FT, $CDCl_3$) νmax: 3690, OH; 3500, 3700, bs, OH; 1764, 1730, ester C=O; 1668, 1636, quinone C=O; 1601, C=C. HRMS calculated for $C_{22}H_{18}O_9$: [M+·] 425.0951 found 425.0948.

Step 8: **(1'S,1R,3S) and (1'S,1S,3R) Ethyl [11-hydroxy-6-acetoxy-1-(2',3',6'-trideoxy-3'-trifluoroacetamido-4'-O-p-nitrobenzoyl-L-lyxohexopyranose) 5,12-dioxo-3,4,5,12-tetrahydroanthraceno (2,3-C) pyran-3-yl] formate**

These compounds were obtained in 61% yield by following the same procedure as described in example 1, step 10 and using the aglycone from step 7 above. (MP: 155-158°C of 1'S,1S,3R and 182-184°C of 1'S,1R,3S). ^1H NMR (200 MHz, $CDCl_3$) of the less polar (1'S,1S,3R) diastereomer, δ: 1.26 (d, 3H, J=6.5 Hz, H_3C-6'), 1.39 (t, 3H, J=7.1 Hz, CH_3), 2.21 (m, 2H, H_2C-2'), 2.54 (s, 3H, O=C-CH_3), 2.88 (m, 1H, HCHaCHC=O), 3.13 (m, 1H, HCHeCHC= O), 4.37 (q, 2H, J=7.1 Hz, OCH_2), 4.49 (broad q, 1H, J=6.5 Hz, HC-5'), 4.67 (m, 1H, HC- 3'), 4.83 (dd, 1H, J=11.6, 4.45 Hz, OCHC=O), 5.49 (broad s, 1H, HC-4'), 5.77 (broad s, 1H, Wh<6 Hz, HC-

1'), 6.21 (s, 1H ,O-CH-O), 6.24 (d, 1H, J=9.1 Hz, NH), 7.84 (m, 2H, ArH), 8.60 (m, 2H, ArH), 8.33 (dd, 4H, p-nitroaryl-H), 13.54 (s, 1H, exchangeable, OH). ^{1}H NMR (200 MHz, $CDCl_3$) of the (1'S,1R,3S) diastereomer δ: 1.29 (d, 3H, J=6.5 Hz, H_3C-6'), 1.37 (t, 3H, J=7.1 Hz, CH_3), 2.08 (m, 2H, H_2C-2'), 2.88 (broad m, 1H, HCHaCHC-O), 3.11 (broad m, 1H, HCHeCHC=O), 4.25 (q, 2H, J= 7.0 Hz, OCH_2), 4.67 (m, 1H, HC-3'), 4.81 (m, 1H, HC-5'), 4.85 (m, 1H, OCHC=O), 5.45 (broad s, 1H, HC-4'), 5.71 (broad s, 1H, H-C-1'), 6.37 (broad d, 1H, J=9 Hz, NH), 6.39 (s, 1H, O-CH-O), 7.85 (m, 2H, ArH), 8.30 (m, 2H, ArH), 8.33 (dd, 4H, p-nitroaryl-H), 13.66 (s, 1H, exchangeable, OH). IR (FT, $CDCl_3$) νmax: 3431, OH; 1737, bs, ester C=O; 1674, quinone C=O; 1595, C=C.

Step 9: **(1'S,1S,3R) and (1'S,1R,3S) Methyl[11-hydroxy-1-(2', 3',6'-trideoxy-3'-trifluoroacetamido-4'-hydroxy-L-lyxohexopyranose)-5,12-dioxo-3,4,5,12-tetrahydro-anthraceno[2,3-c]pyran-3-yl]formate, BCH-692 and BCH-691 respectively.**

Deprotection as described in example 1, step 11 (done at room temperature) gave the titled compounds in 65% yield. The less polar component was assigned to BCH-692. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.31 (d, 3H, J=6.6 Hz, CH_3), 1.87 (dt, 1H, J=3.8, 13.5 Hz, 2'-HCHa), 2.04 (dd, 1H, J=5.2, 13.4 Hz, 2'-HCHe), 2.76 (dd, 1H, J=11.8, 19.5 Hz, HCHa), 3.18 (dd, 1H, J=3.9, 19.5 Hz, HCHe), 3.64 (bs, 1H, 4'-CH), 3.87 (s, 3H, OCH_3), 4.23 (bq, 1H, J=6.6 Hz, 5'-CH), 4.39 (m, 1H, 3'-CH), 4.75 (dd, 1H, J=3.9, 11.8 Hz, O-CH), 5.59 (bd, 1H, J=3.5 Hz, 1'-CH), 6.02 (s, 1H, O-CH-O), 6.71 (bd, 1H, J=9.1 Hz, NH), 7.72 (m, 2H, ARH), 7.96 (M, 1H, ArH), 8.15 (s, 1H, ArH), 8.48 (m, 1H, ArH), 13.75 (s, 1H, ArOH).

The more polar component was assigned to BCH-691. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40 (d, 3H, J=6.6 Hz, CH_3), 1.88

(m, 2H, 2'-CH_2), 2.75 (dd, 1H, J=11.7, 19.7 Hz, HC<u>Ha</u>), 3.17 (dd, 1H, J=4.1, 19.7 Hz, HC<u>He</u>), 3.64 (bs, 1H, 4'-CH), 3.85 (s, 3H, OCH_3), 4.31 (m, 1H, 3'-CH), 4.58 (bq, 1H, J=6.7 Hz, 5'-CH), 4.71 (dd, 1H, J=4.1, 11.6 Hz, O-CH), 5.49 (bs, 1H, 1'-CH), 6.19 (s, 1H, O-CH-O), 6.72 (bd, 1H, J=7.9 Hz, NH), 7.70 (m, 2H, ArH), 7.97 (bd, 1H, J=7.4 Hz, ArH), 8.17 (s, 1H, ArH), 8.47 (bd, 1H, J=7.4 Hz, ArH), 13.8 (s, 1H, ArOH). Small amounts of BCH-673 (5-10%) could also be obtained. The spectral data was similar as the one obtained with BCH-691 except for the presence of the ethyl ester group.

<u>Step 10:</u> (1'S,1S,3R) and 1'S,1R,3S) Methyl(11-hydroxy-6-methoxy- 1-[2',3',6'-trideoxy-3-trifluoroacetamido-4'-hydroxy- L-lyxohexopyranose]-5,12-dioxo-3,4,5,12-tetrahydroanthra- ceno[2,3-c]pyran-3-yl)formate, BCH-674 and BCH-675 respectively.

Deprotection was done as described in step 9 above but at -15°C. BCH-674 is assigned to the compound giving the following data: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.33 (d, 3H, J=6.6 Hz, CH_3), 1.89 (m, 2H, 2'-CH_2), 2.89 (dd, 1H, J=12.2, 18.6 Hz, HC<u>Ha</u>), 3.31 (dd, 1H, J=4.2, 18.6 Hz, HC<u>He</u>), 3.62 (bs, 1H, 4'-CH), 3.85 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.35 (m, 1H, 3'-CH), 4.53 (bq, 1H, J=6.6 Hz, 5'-CH), 5.49 (bs, 1H, 1'-CH), 6.25 (s, 1H, O-CH-O), 6.76 (bd, 1H, NH), 7.82 (m, 2H, ArH), 8.24 (m, 2H, ArH), 12.54 (s, 1H, ArOH).

BCH-675 was assigned to the compound which gave the following data: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.28 (d, 3H, J=6.6 Hz, CH_3), 1.87 (m, 1H, 2'-HC<u>Ha</u>), 2.04 (m, 1H, 2'-HC<u>He</u>), 2.86 (dd, 1H, J=12.1, 18.4 Hz, HC<u>Ha</u>), 3.32 (dd, 1H, J=3.9, 18.3 Hz, HC<u>He</u>), 3.63 (bs, 1H, 4'-CH), 3.86 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.20 (bq, 1H, J=6.6 Hz, 5'-CH), 4.33 (m, 1H, 3'-CH), 4.83 (dd, 1H, J=3.9, 12.1 Hz, O-CH), 5.51 (bs, 1H, 1'-CH), 6.13 (s, 1H, O-CH-O), 6.75 (bd, 1H,

J=8 Hz, NH), 7.27 (m, 2H, ArH), 8.27 (m, 2H, ArH), 13.6 (s, 1H, ArOH).

Step:11 (1'S,1R,3S) and (1'S,1S,3R)-(6-hydroxy-5,12-dioxo-1-(3'-trifluoroacetamido-1-daunosaminyl)-3,4,5,12-tetrahydro-anthraceno[2,3-C]pyran-3-yl)formate

Under argon, a (28°C) solution containing 196 mg (0.25 mmol) of glycoside from step 4 above in 50 ml of dry methanol was treated with a total of 5 equivalent (0.25 ml) of a 4.37 M, $NaOCH_3$ methanolic solution which were added according to the progress of the reaction. The reaction mixture was then quenched with 10 ml of saturated aqueous NH_4Cl and extracted with dichloromethane (2x50 ml). The combined organic layers were washed with water (2x75 ml) and dried (Na_2SO_4). Purification by HPLC gave 7.8 mg (5% yield) of the 1'S,1R,3S diastereomer, BCH-681, (MP: 200°C dec.). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.35 (t, 3H, J=7.1 Hz, $CH_2C\underline{H}_3$), 1.42 (d, 3H, J=6.6 Hz, H_3C-6'), 1.89 (2H, HaC-2' and HeC-2'), 2.76 (dd, 1H, J=19.6, 11.4 Hz, HC$\underline{Ha}$CHC=O), 3.19 (dd, 1H, J=19.6, 4.1 Hz, HC$\underline{He}$CHC=O), 3.64 (broad s, 1H, HC-4'), 4.31 (q, 2H, J=7.2 Hz, O$\underline{CH_2}CH_3$), 4.32 (m, 1H, HC-3'), 4.61 (bq, 1H, J=6.5 Hz, HC-5'), 4.69 (dd, 1H, J=11.8 and 4.2 Hz, O-CH), 5.48 (broad s, 1H, HC-1'), 6.17 (s, 1H, O-CH-O), 6.73 (broad d, 1H, NH), 7.74 (m, 2H, ArH), 7.96 (m, 1H, ArH), 8.13 (s, 1H, ArH), 8.51 (m, 1H, ArH), 13.83 (s, 1H, Ar-OH).

The 1'S, 1S, 3R diastereomer, BCH-684, was also obtained with 2% yield (2.9 mg). (MP: 175°C melt and dec.). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.32 (d, 3H, J=6.6 Hz, H_3C-6'), 1.38 (t, 3H, J=7.2 Hz, $OCH_2C\underline{H}_3$), 1.85 (m, 1H, HaC-2'), 2.02 (m, 1H, HeC-2'), 2.62 (dd, 1H, J=19.5, 11.8 Hz, HC$\underline{Ha}$CHC=O), 3.21 (dd, 1H, J=19.5, 4.0 Hz, HC$\underline{He}$CHC=O), 3.65 (broad s, 1H, HC-4'), 4.25 (bq, 1H, HC-5'), 4.35 (m, 3H,

$OC\underline{H}_2CH_3$ and HC-4'), 4.75 (dd, 1H, J=12.0, 3.8 Hz, OCHC=O), 5.61 (broad s, 1H, HC-1'), 6.02 (s, H, O-CH-O), 6.72 (broad d, 1H, NH), 7.75 (m, 2H, ArH), 7.98 (m, 1H, ArH), 8.12 (s, 1H, ArH), 8.52 (m, 1H, ArH), 13.86 (s, 1H, Ar-OH).

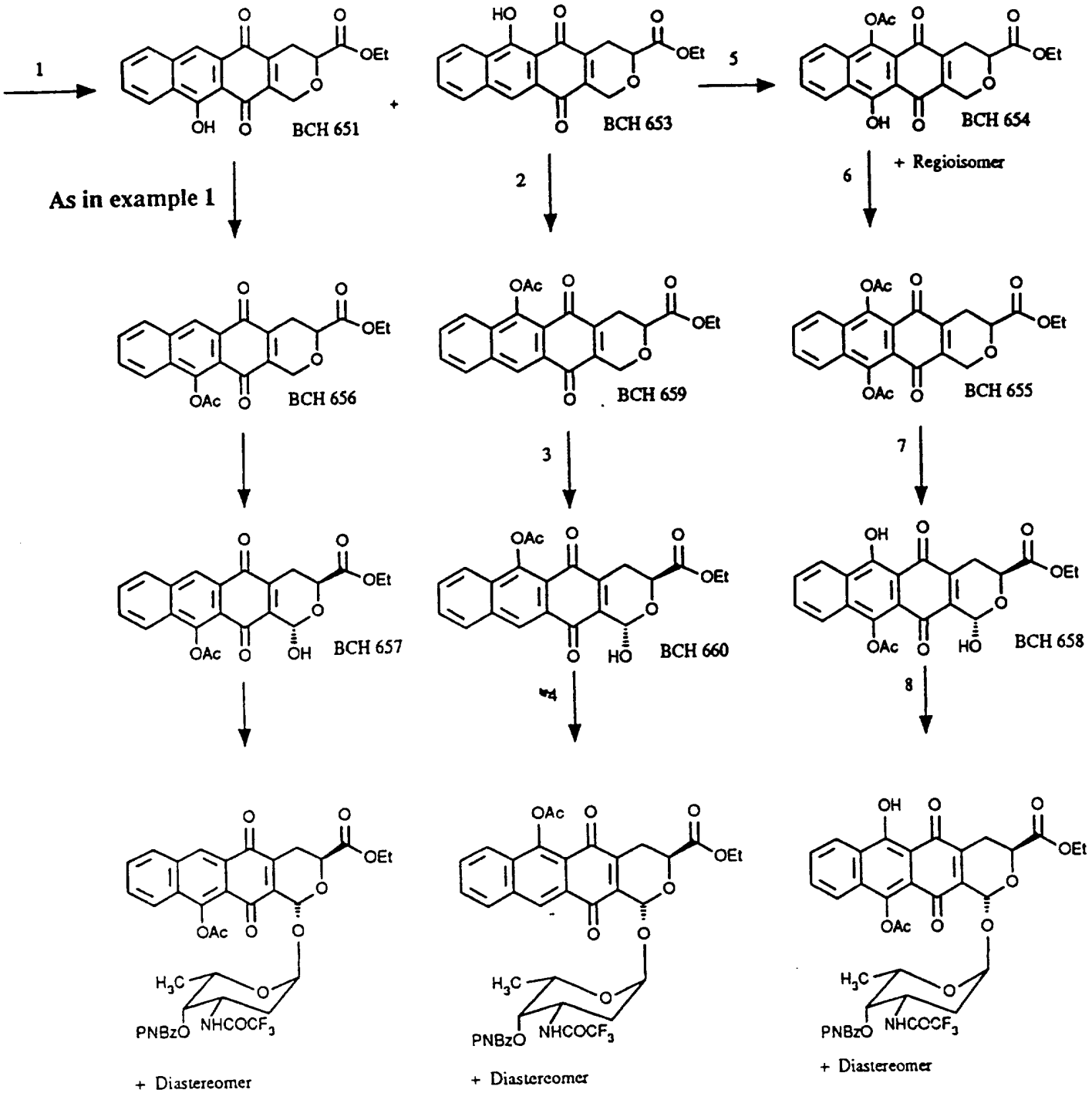
BCH-706 could be isolated by HPLC in 2% yield. Its NMR spectrum is similar to the one obtained from BCH-684 except for the presence of a proton signal for the methoxy ester group at 3.87 ppm instead of signals for the ethyl ester.

BCH-683 was also obtained in 17% yield and was assigned to the compound giving the following data. (MP: 190-215°C dec.)
^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.41 (d, 3H, J=6.6 Hz, CH_3), 1.89 (m, 2H, 2'-CH_2), 2.78 (dd, 1H, J=11.8, 19.2 Hz, HC$\underline{H}$a), 3.20 (dd, 1H, J=4.0, 19.6 Hz, HC$\underline{H}$e), 3.66 (bs, 1H, 4'-CH), 3.87 (s, 3H, OCH_3), 4.34 (m, 1H, 3'-CH), 4.63 (bq, 1H, J=6.6, 5'-CH), 4.73 (dd, 1H, J=4.0, 11.8 Hz, O-CH), 5.49 (bs, 1H, 1'-CH), 6.18 (s, 1H, O-CH-O), 6.77 (bd, 1H, J=7.1 Hz, NH), 7.74 (m, 2H, ArH), 7.98 (dd, 1H, J=2.4, 7.1 Hz, ArH), 8.14 (s, 1H, ArH), 8.52 (dd, 1H, J=2.4, 7.1 Hz, ArH), 13.8 (s, 1H, ArOH).

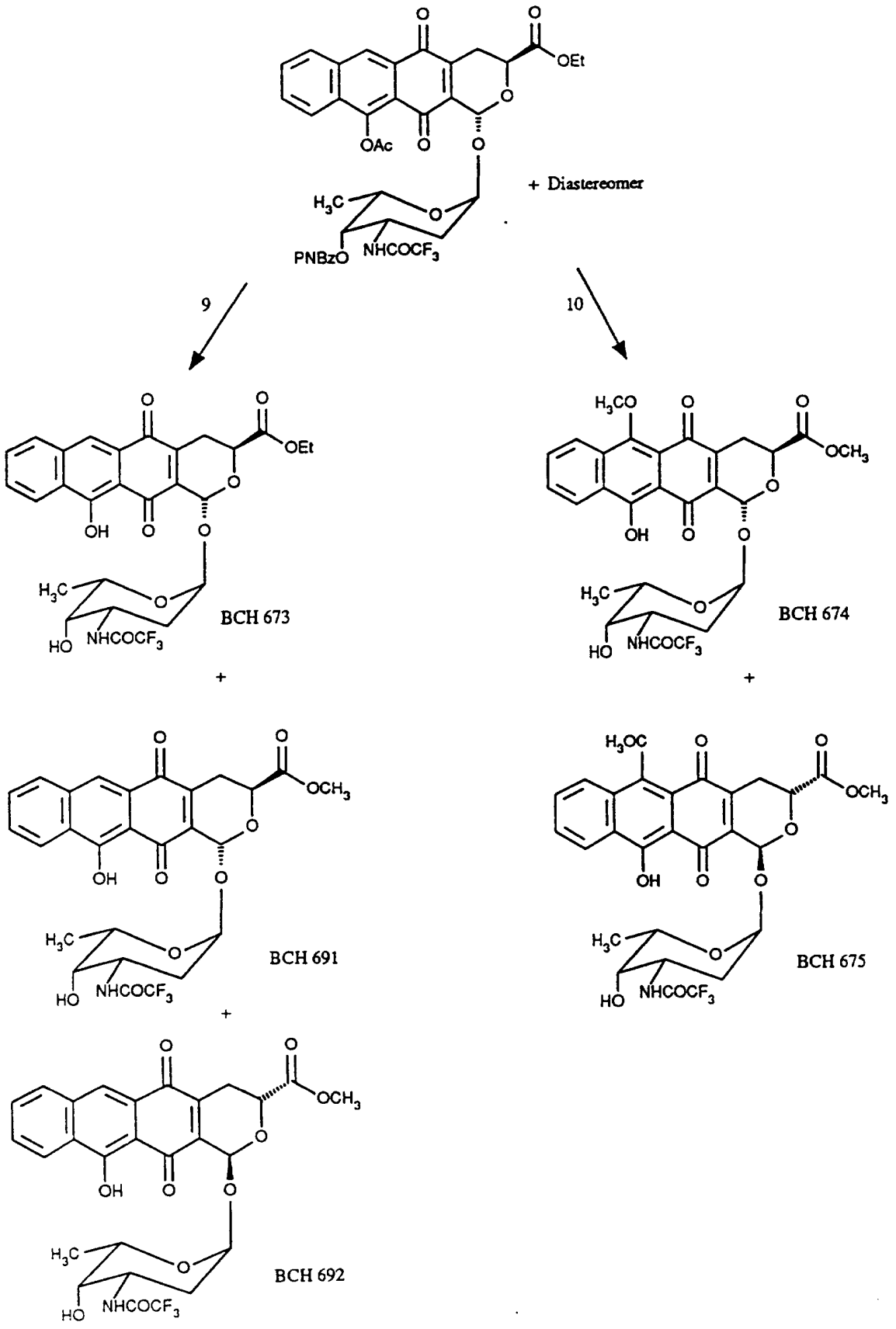
Step 12: (1'S,1R,3S) and (1'S,1S,3R) Ethyl(6-hydroxy-11-methoxy-5,12-dioxo-1-(3'-trifluoroacetamido-1-daunosaminyl)-3,4,5,12-tetrahydroanthraceno[2,3-c]pyran-3-yl)formate

The reaction from step 11 above, carried out at -15°C, yielded (20% yield) a mixture of 1'S,1R,3S and 1'S,1S, 3R ethyl (6-hydroxy-11-methoxy-5,12-dioxo-1-(3'-trifluoroaceta-mido-1-daunosaminyl)-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl) formate. (MP: 176-180°C). ^{1}H NMR (300 MHz, $CDCl_3$) of the (1'S, 1R, 3S) diastereomer δ: 1.34 (d, 3H, J=6.6 Hz, H_3C-6'), 1.38 (t, 3H, J=7.1 Hz, $OCH_2C\underline{H}_3$), 1.90 (m, 1H, HaC-2'), 2.04 (m, 1H,

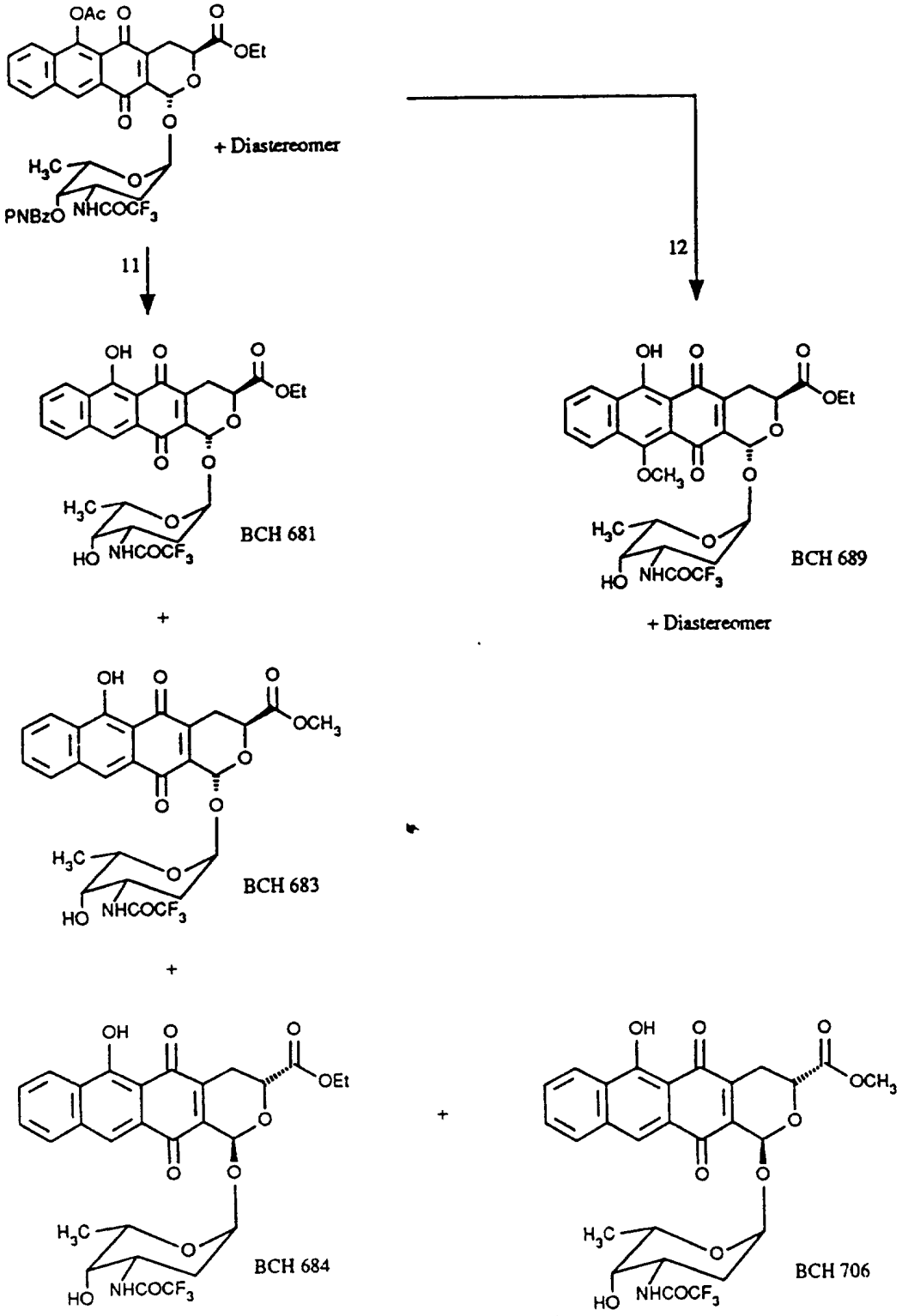
Example 3: Preparation of various pyrano modified heteroanthracyclinones and heteroanthracyclines



Example 3 : (Continued)



Example 3 : (Continued)



HeC-2′), 2.94 (dd, 1H, J=18.7, 12.2 Hz, HC<u>H</u>aCHC=O), 3.33 (dd, 1H, J=18.4, 3.3 Hz, HC<u>H</u>eCHC=O), 3.65 (broad S, 1H, HC-4′), 3.95 (s, 3H, $ArOCH_3$), 4.35 (q, 2H, J=7.1 Hz, $OC\underline{H}_2CH_3$), 4.42 (m, 1H, HC-3′), 4.68 (bq, 1H, HC-5′), 4.78 (dd, 1H, J=11.9, 4.2 Hz, O-CH), 5.53 (broad s, 1H, HC-1′), 6.34 (s, 1H, O-CH-O), 6.76 (broad d, 1H, NH), 7.83 (m, 2H, ArH), 8.31 (m, 2H, ArH), 13.70 (s, 1H, ArOH). ^1H NMR (300 MHz, $CDCl_3$) of the 1′S, 1S, 3R diastereomer δ: 1.31 (d, 3H, J=6.6 Hz, H_3C-6′), 1.38 (t, 3H, J=7.1 Hz, $OCH_2C\underline{H}_3$, 1.90 (m, 1H, HaC-2′), 2.04 (m, 1H, HeC-2′), 2.91 (dd, 1H, J=18.2, 12.0 Hz, HC<u>H</u>aCHC=O), 3.34 (dd, 1H, J=18.3, 3.7 Hz, HC<u>H</u>eCHC=O), 3.65 (broad s, 1H, HC-4′), 3.94 (s, 3H, $ArOCH_3$), 4.28 (bq, 1H, HC-5′), 4.35 (q, 2H, J=7.1 Hz, $OC\underline{H}_2CH_3$), 4.42 (m, 1H, HC-3′), 4.81 (dd, 1H, J=12.4, 4.0 Hz, O-CH), 5.59 (broad s, 1H, HC-1′), 6.14 (s, 1H, O-CH-O), 6.74 (broad d, 1H, NH), 7.83 (m, 2H, ArH), 8.31 (m, 2H, ArH), 13.59 (s, 1H, ArOH).

EXAMPLE 4

<u>Step 1:</u> p-nitrobenzyl (5,8-dioxo-5,8-dihydroisochroman-3-yl) formate

p-Nitrobenzyl 5,8-dimethoxy-isochroman-3-yl formate was oxidized as described in example 2, step 3. The titled compound was obtained in 92% yield. (MP:133°C decomposes) ^1H NMR (200 MHz $CDCL_3$) δ: 2.70 (ddt, 1H, J=18.7, 9.0, 3.0 Hz, HC<u>H</u>aCHC=O), 2.95 (d multiplet, 1H, J=19.0 Hz, HC<u>H</u>eCHC=O), 4.38 (dd, 1H, J=8.9, 4.3 Hz, OCHC= O), 4.56 (dt, 1H, J=17.1, 3.0 Hz, HC<u>H</u>a-O), 4.88 (ddd, 1H, J=17.3, 2.8, 1.7 Hz, HC<u>H</u>e-O), 5.36 (broad s, 2H, CH_2 ArH), 6.79 (dd, 2H, ArH), 7.57 (d, 2H, ArH), 8.29 (d, 2H, ArH).

Step 2: p-nitrobenzyl [5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl]formate

A solution containing 669 mg (1.9 mmol) of pyranoquinone from step 1, 485 mg (2.9 mmol) of 3,6-dihydrobenzo [b]-1,2-oxathiin-2-oxide (Charlton U.L. and Durst T., Tet. Lett., 25, 5287, 1984) in 50 ml of xylenes was refluxed overnight. The solvent was then removed in vacuo. The residue was flash chromatographed with ethyl acetate in toluene and gave 536 mg (62%) of the titled pyranoanthraquinone. (MP: 214-215°C decomposes) ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.84 (ddt, 1H, J=18.9, 9.0, 2.7 Hz, HCHaCHC=O), 3.12 (broad d, 1H, J=19.0 Hz, HCHeCHC=O), 4.40 (dd, 1H, J=9.1, 4.4 Hz,OCHC= O), 4.67 (dt, 1H, J=19.0, 3.0 Hz, HCHa-O), 5.04 (broad d, 1H, J=18.9Hz, HCHe-O), 5.33 (broad s, 2H, $ArCH_2$), 7.53 (d, 2H, ArH), 7.67 (m, 2H, ArH), 8.04 (m, 2H, ArH) 8.21 (d, 2H, ArH), 8.58 (s, 1H, ArH, 8.62 (s, 1H, ArH).

Step 3: (1S, 3S) and (1R, 3R) p-nitrobenzyl [1-hydroxy-5,12-dioxo-3, 4, 5, 12- tetrahydroanthraceno [2,3-c] pyran- 3-yl] formate

A mixture containing 164 mg (0.37 mmol) of the pyranoanthra-cyclinone from step 2, 65 mg (0.37 mmol) of N-bromosuccinimide and 10 mg of AIBN in 25 ml of CCl_4 was refluxed for 2 hours. The solvent was then removed and the residue was stirred with 35 ml of a 7:3 solution of THF in water for ten hours. The mixture was then extracted three times with 25 ml aliquots of CH_2Cl_2. The combined organic layer was washed once with 10 ml of water, 10 ml of brine, and then dried over $NaSO_4$. After evaporation of solvents, flash chromatography of the residue gave 118 mg (69%) of the desired pyranoanthraquinone aglycone. (MP: 275°C decomposes) ^{1}H NMR (200 MHz, DMSO-d_6) δ: 2.68 (dd, 1H,

J=19.1, 11.5 Hz, HCHaCHC=O), 3.00 (dd, 1H, J=19.4, 4.4 Hz, HCHeCHC=O), 4.89 (dd, 1H, J=11.4, 4.1 Hz, OCHC=O), 5.39 (broad s, 2H, $ArCH_2$), 5.98 (d, 1H, J=6.3 Hz, CHOH), 7.40 (d, 1H, J=6.1, exchangeable OH), 7.7 (d, 2H, ArH), 7.8 (m, 2H, ArH), 8.27 (d, 2H, ArH), 8.29 (m, 2H, ArH), 8.66 (s, 1H, ArH), 8.67 (s, 1H, ArH).

Step 4: **(1'S, 1R, 3S) and (1'S, 1S, 3R)-p-nitrobenzyl [1-(2',3',6'-trideoxyacetamido-4'-O-p-nitrobenzoyl-L- lyxohexopyranose)-5,12-dioxo-3,4,5,12-tetrahydroanthra-ceno [2,3-c]pyran-3-yl]formate**

These glycosides were obtained by the same procedure as described in step 10 of example 1 and by using the aglycone from step 3 of this example. (MP: 192-195°C for 1'S,1S,3R and 173-174°C for 1'S,1R,3S). ^1H NMR (200 MHz,$CDCl_3$) of the (1'S,1S,3R) diastereomer, δ: 1.12 (d, 3H, J=6.3 Hz, H_3C-6'), 2.09 (m, 2H, H_2C-2'), 2.83 (dd, 1H, J=19.4, 11.7 Hz, HCHaCHC=0), 3.26 (dd, 1H, J=19.1, 3.7 Hz, HCHeCHC=O), 4.4 (broad q, 1H, J=6.1 Hz, HC-5'), 4.65 (m, 1H, HC-3'), 4.89 (dd, 1H,J= 11.8, 3.6 Hz, OCHC=O), 5.42 (broad s, 3H, HC-4' and $aralCH_2$), 5.82 (broad s, 1H, W_h<6Hz, HC-1'), 6.13 (s, 1H, W_h<0.7 Hz, OCH-O), 6.40 (d, 1H, J=7.3 Hz, NH), 7.28 (d, 2H, p-nitrobenzyl-H), 7.73 (m, 2H, ArH), 8.09 (m, 2H, ArH), 8.29 (d, 2H, p-nitrobenzyl-H), 8.31 (dd, 4H, benzoyl H), 8.64 (s, 1H, ArH), 8.69 (s, 1H, ArH). ^1H NMR (200 MHz, $CDCl_3$) of the (1'S,1R,3S) diastereomer, δ: 1.42 (d, 3H, J=6.4 Hz, H_3C-6'), 2.09 (m, 2H, H_2C-2'), 2.85 (dd, 1H, J=19.4, 11.3 Hz, HCHaCHC=O) 3.25 (dd, 1H, J=19.4, 4.3 Hz, HCHeCHC=O), 4.63 (m, 1H, HC-3'), 4.84 (overlaped, m, 2H, HC-5' and OCHC=O), 5.41 (broad s, 2H, $aralCH_2$), 5.47 (s, 1H, W_h=5 Hz, HC-4'), 5.69 (s, 1H, W_h<0.7Hz, O-CH-O), 6.57 (d, 1H, J=7.2 Hz, NH) 7.73 (d, 2H, p-nitrobenzyl-H), 7.75 (m, 2H, ArH), 8.11 (m, 2H, ArH), 8.33 (d, 2H, p-nitrobenzyl-H), 8.37 (dd, 4H, p-nitrobenzoyl-H), 8.69 (s, 1H, ArH).

Step 5: (1'S,1S,3S) Methyl (1-[2',3',6'-trideoxyacetamido-4'- hydroxy-L-lyxohexopyranose]-5,12-dioxo-3,4,5,12-tetrahydroantraceno[2,3-c]pyran-3-yl)formate - BCH-672

Deprotection of the less polar glycoside, from step 4 above, by using the method described in example 1, step 11, gave the titled compound in 20% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.29 (d, 3H, J=3.3 Hz, CH_3), 1.85 (dt, 1H, J=3.8, 13.3 Hz, 2'-HCHa), 2.00 (dd, 1H, J=5.4, 13.4 Hz, 2'-HCHe), 2.76 (ddd, 1H, J=1.0, 11.8, 19.5 Hz, HCHa), 3.18 (dd, 1H, J=3.8, 19.5 Hz, HCHe), 3.63 (bs, 1H, 4'-CH), 3.86 (s, 3H, OCH_3), 4.23 (bq, 1H, J=6.6 Hz, 5'-CH), 4.35 (m, 1H, 3'-CH), 4.75 (dd, 1H, J=3.9, 11.8 Hz, O-CH), 5.61 (bd, 1H, J=3.4 Hz, 1'-CH), 6.04 (s, 1H, O-CHO), 6.71 (bd, 1H, J=9.0 Hz, NH), 7.70 (m, 2H, ArH), 8.06 (m, 2H, ArH), 8.60 (s, 1H, ArH), 8.67 (s, 1H, ArH).

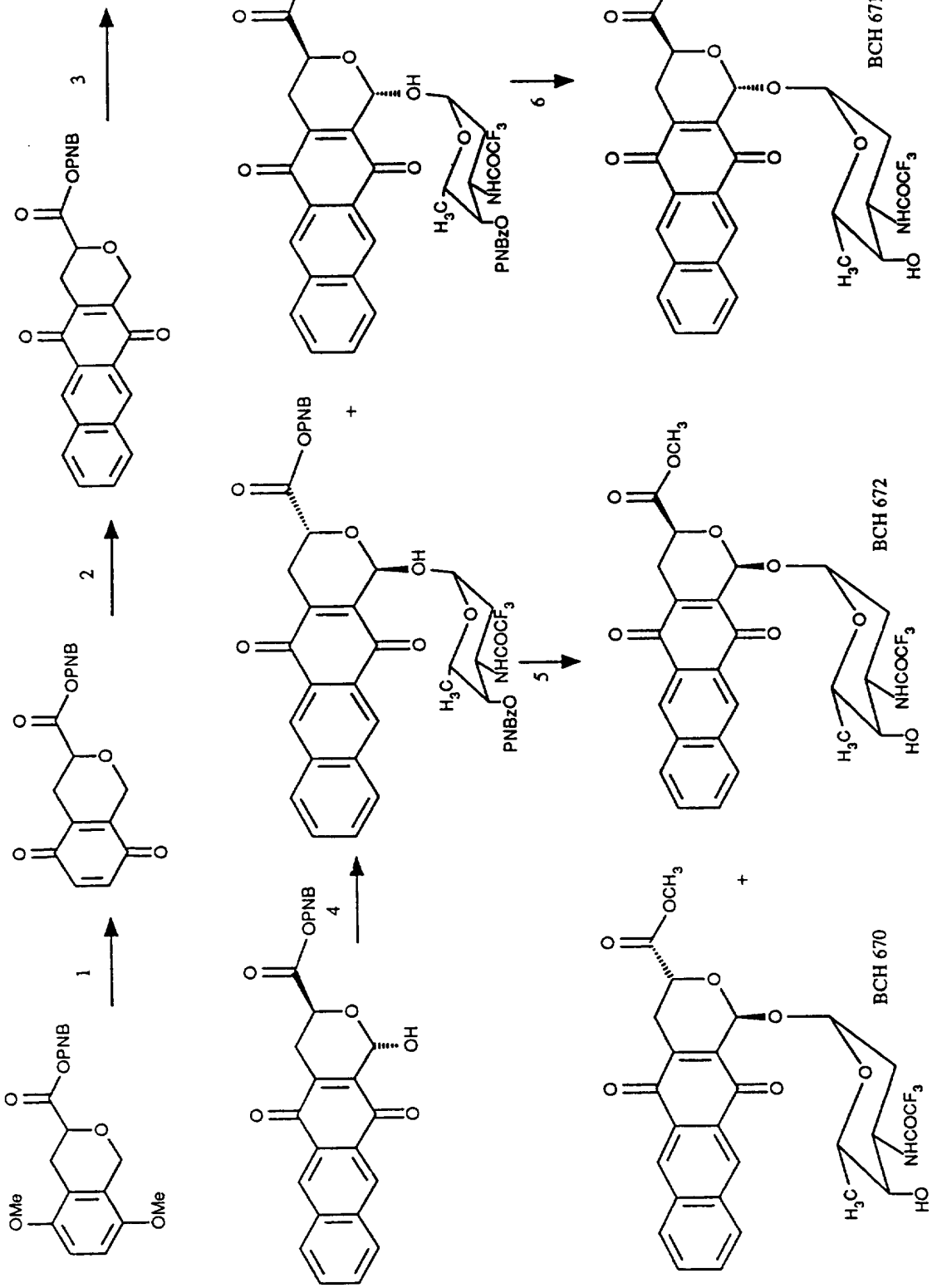
A second less polar component, tentatively assigned as (1'S 1S, 3R) methyl (1-[2',3',6'-trideoxyacetamido-4'-hydroxy-L-lyxo-hexopyranose]-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-C] pyran-3-yl)formate, BCH-670, was obtained in 60% yield.

^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.25 (d, 3H, J=6.6 Hz, CH_3), 1.86 (dt, 1H, J=3.84, 13.2, 2'-HCHa), 2.09 (dd, 1H, J=5.2, 13.4 Hz, 2'-HCHe), 2.51 (dd, 1H, J=11.9, 15.2 Hz, HCHa), 2.88 (dd, 1H, J=2.9, 15.2 Hz, HCHe), 3.61 (bd, 1H, J=4.2 Hz, 4'-CH), 3.82 (s, 3H, OCH_3), 4.21 (bq, 1H, J=6.8 Hz, 5'-CH), 4.44 (m, 1H, 3'-CH), 4.57 (dd, 1H, J=2.74, 11.87 Hz, O-CH), 5.53 (bd, 1H, J=3.6 Hz, 1'-CH), 6.19 (s, 1H, O-CH-O), 7.67 (bd, 1H, J=8.6 Hz, NH), 7.71 (m, 2H, ArH), 8.06 (m, 2H, ArH), 8.57 (s, 1H, ArH), 8.58 (s, 1H, ArH).

Step 6: (1'S,1R,3S) Methyl (1-[2',3',6'-trideoxyacetamido-4'- hydroxy-L-lyxohexopyranose]-5,12-dioxo-3,4,5,12-tetrahydroanthraceno(2,3-c)pyran-3-yl)formate, BCH-671.

Deprotection of the more polar glycoside, from step 4 above by using the method described in example 1, step 11, gave BCH-671 in 70% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.41 (d, 3H, J=6.6 Hz, CH_3), 1.93 (m, 2H, 2'-CH_2), 2.51 (dd, 1H, J=12.0, 15.1 Hz, HCHa), 2.85 (dd, 1H, J=3.0, 15.1 Hz, HCHe), 3.65 (bs, 1H, 4'-CH), 3.80 (s, 3H, OCH_3), 4.46 (overlapped m, 3H, 3',5'-CH and O-CH), 5.42 (bd, 1H, J=3.2 Hz, 1'-CH), 6.32 (s, 1H, O-CH-O), 6.69 (bd, 1H, J=8.3 Hz, NH), 7.70 (m, 2H, ArH), 8.05 (m, 2H, ArH), 8.57 (s, 1H, ArH) 8.58 (s, 1H, ArH).

Example 4 : Preparation of (1'S, 1S, 3R) and (1'S, 1R, 3S) methyl [1-(2', 3', 6'-trideoxy-trifluoroacetamido-4'-hydroxy-L-lyxohexo-pyranose)-5,-12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate



EXAMPLE 5

Step 1: 5,8-dimethoxy-1-methylbenzo[C]1,2-oxathiin-2-oxide

Following a slight modification of Durst and Charlton procedure (Tel. Lett., 25 (46), 5290, 1984), 800 ml of a 2.5 M solution of methyl lithium in hexanes was added, at room temperature and under argon, to a solution containing 14.38 g (59 mmol) of hydroxysulfone from "example 1 - step 3" in 2.5 l of anhydrous THF. After stirring for 16 hours, 400 ml of methanol was added to the mixture. Solvents were removed under vaccuo and the residue was treated with 500 ml of 12 M HCl at 50°C for 3 min. The solution was then diluted in 1 l of water and extracted three times with 300 ml of dichloromethane. The combined organic layer was washed twice with water, once with brine and dried over $MgSO_4$. After removal of solvents, flash chromatography of the residue gave the titled sultine as a yellow solid in 47% yield. (MP: 152°- 153°C). ^1H NMR (200 MHz, $CDCl_3$) δ:1.58 (d, 3H, J=6.2 Hz, CH_3), 3.49 (d, 1H, J=14.8 Hz, CH), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.29 (d, 1H, J=14.8 Hz, CH), 5.63 (q, 1H, J=6.2 Hz, $CH_3C\underline{H}$), 6.82 (s, 2H, ArH). CMR (75.44 MHz, $CDCl_3$) δ:15.3, CH_3; 52.2, CH_2; 55.7, OCH_3; 59.9, CH; 110.1, 110.6, aryl CH; 123.6, 123.8, 149.8, 149.9, aryl C. MS (CI, NH_3,137°C). m/e: 246 (100, $M+NH_4$).

Step 2: Cis and trans p-nitrobenzyl (5,8-dimethoxy-1-methyliso- chroman-3-yl) formate

These 1-methylated isochromans were obtained by following the same procedure as described for the isochroman of "example 1, step 5". Thus, the reaction between 4g (16.5 mmol) of the 1-methylated sultine from step 1 above and 18.76g (83 mmol) of p-nitrobenzyl-glyoxalate hydrate resulted in a black residue which after

flash chromatography (10% ethyl acetate - 25% toluene - 65% cyclohexane) gave the two titled diastereomeric isochromans in a 3:1 ratio. The trans isomer (2.8g, 44% yield) had: (MP:110°-111°C). ^{1}H NMR (200 MHz, $CDCl_3$) δ:1.53 (d, 3H, J=6.8 Hz, CH_3), 2.85 (dd, 1H, J=9.8, 16.8 Hz, Hcha), 3.07 (dd, 1H, J= 4.4, 16.7 Hz, HCHe), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.69 (dd, 1H, J=4.7, 9.9 Hz, OCH), 5.29 (q, 1H, J=6.7 Hz, $OCHCH_3$), 5.33 (bs, 2H, OCH_2), 6.68 (s, 2H, H-C= C-H), 7.49 (d, 2H, J=8.9 Hz, ArH), 8.22 (d, 2H, J=8.9 Hz, ArH). CMR (75.44 MHz, $CDCl_3$) δ:19.6, CH_3; 25.5, CH_2; 55.3, 55.4, OCH_3; 65.0, OCH_2; 67.2, 68.6, OCH; 107.8, 123.6, 128.2, aryl CH; 121.0, 128.0, 142.8, 147.6, 149.2, 150.6, aryl C; 171.4, ester C=O.

IR (FT, $CDCl_3$) ^{v}max: 1756, ester C=O, 1216, C-O. MS (CI, NH_3, 191°C) m/e: 405 (52, $M+NH_4$), 270 (100, $M+NH_4-C_7H_5NO_2$). The cis isomer (247) (0.9g, 14% yield, oil) had: ^{1}H NMR (200 MHz, $CDCl_3$) δ:1.62 (d, 3H, J=6.4 Hz, CH_3, 2.73 (ddd, 1H, J=2.1, 11.4, 16.0 Hz, HCHa), 3.17 (dddd, 1H, J=1.2, 2.4, 16.0 Hz, HCHe), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.23 (dd, 1H, J=2.4, 11.4, OCH), 5.09 (bq, 1H, J=6.5 Hz, $CHCH_3$), 5.36 (bs, 2H, OCH_2), 6.71 (bs, 2H, ArH), 7.80 (d, 2H, J=8.9 Hz, ArH), 8.25 (d, 2H, J=8.9 Hz, ArH). CMR (75.44 MHz, $CDCl_3$) δ:21.5, CH_3; 26.7, CH_2; 55.2, 55.6, OCH_3; 65.0, OCH_2, 71.5, 72.1, OCH; 108.4, 123.7, 128.3, aryl CH_2; 107.9, 122.9, 142.8 148.1, 149.9, 150.4, aryl C; 170.8, ester C=O. IR (FT, $CDCl_3$) ^{v}max: 1755, ester C=O, 1219, C=O. HRMS calculated for $C_{20}H_{21}NO_7$ 387.1318 found 387.1299.

Step 3: **Cis-p-nitrobenzyl(5,8-dioxo-1-methyl-3,4,5,8-tetrahy-drobenzo [2,3-c]pyran-3-yl) formate**

To 400 mg (1.0 mmol) of the cis isochroman from step 2 above in 10 ml of acetonitrile was added, dropwise over 5 min and with stirring, a solution containing 1.96 g (3.6 mmol) of ceric ammonium nitrate in 10 ml of water. After

five minutes the mixture was diluted with 25 ml of water and then extracted three times with 50 ml of methylene chloride. The combined organic layer was washed once with 50 ml of water, once with 25 ml of brine, and then dried over $MgSO_4$. Following evaporation of solvent, the oily yellow residue was found to be pure (95% yield) isochromandione. Flash chormatography, with 20% ethyl acetate in toluene, reduced the yield (65%) considerably without significantly increasing the purity. ^1H NMR (200 MHz, $CDCl_3$) δ:1.57 (d, 3H, J=6.7 Hz, CH_3), 2.57 (ddd, 1H, J= 4.3, 10.8, 18.4 Hz, HCHa), 2.98 (bdt, 1H, J= 2.8, 18.4 Hz, HCHe), 4.19 (dd, 1H, J=2.75, 10.8 Hz, O-CH), 4.81 (m, 1H, $OCHCH_3$), 5.36 (bs, 2H, OCH_2), 6.76 (dd, 2H, J=10.1 Hz, ArH), 7.57 (d, 2H, J=9.0 Hz, ArH), 8.24 (d, 2H, J=9.0 Hz, ArH). CMR (75.44 MHz, $CDCl_3$) δ:20.2, CH_3; 25.2, CH_2; 65.3, OCH_2; 70.2, 71.1, OCH; 123.6, 128.4, aryl CH; 135.7, 136.8, CH; 138.4, 142.2, 143.4, 147.6, quaternary C; 169.2, ester C=O; 185.2, 185.4, quinone C=O.

Step 4: **Trans-p-nitrobenzyl (5,8-dioxo-1-methyl-5,8-dihydro-isochroman-3-yl) formate**

Oxydative demethylation of 160 mg (0.4 mmol) of trans-p- nitrobenzyl (5,8-dimethoxy-1-methylisochroman-3-yl) formate with 780 mg (1.4 mmol) of ceric ammonium nitrate, as described in step 3 above, give 137 mg of the titled isochromandione as a yellow oil. ^1H NMR (200 MHz, $CDCl_3$) δ:1.5 (d, 3H, J=6.8 Hz, CH_3), 2.67 (ddd, 1H, J=2.2, 8.9, 19.0 Hz, HCHa), 2.89 (ddd, 1H, J=1.3, 4.6, 19.0 Hz, HCHe), 4.59 (dd, 1H, J=4.7, 8.9 Hz, OCH), 5.04 (bq, 1H, J=6.8 Hz, $OCHCH_3$), 5.33 (bs, 2H, OCH_2), 6.75 (dd, 2H, J=10.1 Hz, H-C=C-H), 7.54 (d, 2H, J=8.9 Hz, ArH), 8.24 (d, 2H, J= 8.9 Hz, ArH). CMR (75.44 MHz,$CDCl_3$) δ: 19.4, CH_3; 24.4, CH_2; 65.5, OCH_2; 66.7, 67.1, OCH; 123.8, 128.6, 136.0, 136.5, aryl CH; 137.3, 142.2, 143.5, 146.7, aryl C; 185.0, 185.3,

quinone C=O.

Step 5: (1R,3R) and (1S,3S) Cis-p-nitrobenzyl(5,12-dioxo-1-methyl-3,4,5,12-tetrahydroanthraceno(2,3-c)pyran-3-yl)formate

This compound was obtained by following the same procedure as described in "example 4, step 2". Thus, reaction of 250 mg (1.5 mmol) of 3,6-dihydrobenzo-(b)-1,2-oxathin-2-oxide with 268 mg (0.7 mmol) of the cis isochromandione from step 3 above gave 157 mg (49% yield) of the titled tetracycle. (MP: 118°-120°C). ^{1}H NMR (200 MHz, $CDCl_3$ δ:1.69 (d, 3H, J=6.5 Hz, CH_3), 2.74 (ddd, 1H, J=3.7, 10.8, 18.5 Hz, Hc<u>Ha</u>), 3.24 (dt, 1H, J=2.8, 18.5 Hz, HC<u>He</u>), 4.26 (dd, 1H, J=2.9, 10.9 Hz, OCH), 5.04 (m, 1H, C<u>H</u>CH_3), 5.38 (bs, 2H, OCH_2), 7.59 (d, 2H, J=8.9 Hz, ArH), 7.7 (m, 2H, ArH), 8.05 (m, 2H, ArH), 8.26 (d, 2H, J=8.9 Hz, ArH), 8.60 (s, 1H, ArH), 8.61 (s, 1H, ArH), CMR (75.44 MHz, $CDCl_3$) δ:20.6, CH_3; 26.2, CH_2; 65.5, OCH_2; 71.0, 71.4, OCH; 123.9, 128.6, 129.9, 129.7, 130.2, aryl CH; 127.8, 127.9, 128.2, 134.7, 141.1, 142.2, 146.7, 147.2, aryl C; 169.7, ester C=O; 182.2, 182.5, quinone C=O.

Step 6: (1S,3R) and (1R,3S) Trans-p-nitrobenzyl(5,12-dioxo-1-methyl-3,4,5,12-tetrahydroanthraceno[2,3-c]pyran-3-yl)formate

Following the procedure as described in "example 4, step 2", the reaction between 175 mg (1.1 mmol) of 3,6-dihydrobenzo-(b)-1,2-oxathiin-2-oxide with 187 mg (0.5 mmol) of the quinone from step 4 above gave 119 mg (52% yield) of the titled compound. (MP: 131°-132°C). ^{1}H NMR (200 MHz, $CDCl_3$) δ:1.62 (d, 3H, J=6.8 Hz, CH_3), 2.89 (ddd, 1H, J=2.0, 8.9, 19.0 Hz, HC<u>Ha</u>), 3.11 (ddd, 1H, J=1.0, 4.6, 19.1 Hz, HC<u>He</u>, 4.69 (dd, 1H, J=4.7, 8.8 Hz, OCH), 5.30 (bq,

1H, J=6.8 Hz, C<u>H</u>CH_3), 5.35 (bs, 2H, OCH_2), 7.55 (d, 2H, J=8.7 Hz, ArH), 7.7 (m, 2H, ArH), 8.05 (m, 2H, ArH), 8.20 (d, 2H, J=8.7 Hz, ArH), 8.58 (bs, 2H, ArH). CMR (75.44 MHz, $CDCl_3$) δ: 19.6, CH_3; 25.3, CH_2; 65.5, OCH_2; 67.0, OCH; 123.9, 128.7, 128.8, 129.6, 130.2, aryl CH; 127.9, 128.0, 128.2, 134.8, 141.1, 142.3, 146.7, 147.6, aryl C; 170.3, ester C=O; 182.8, 182.9, quinone C=O.

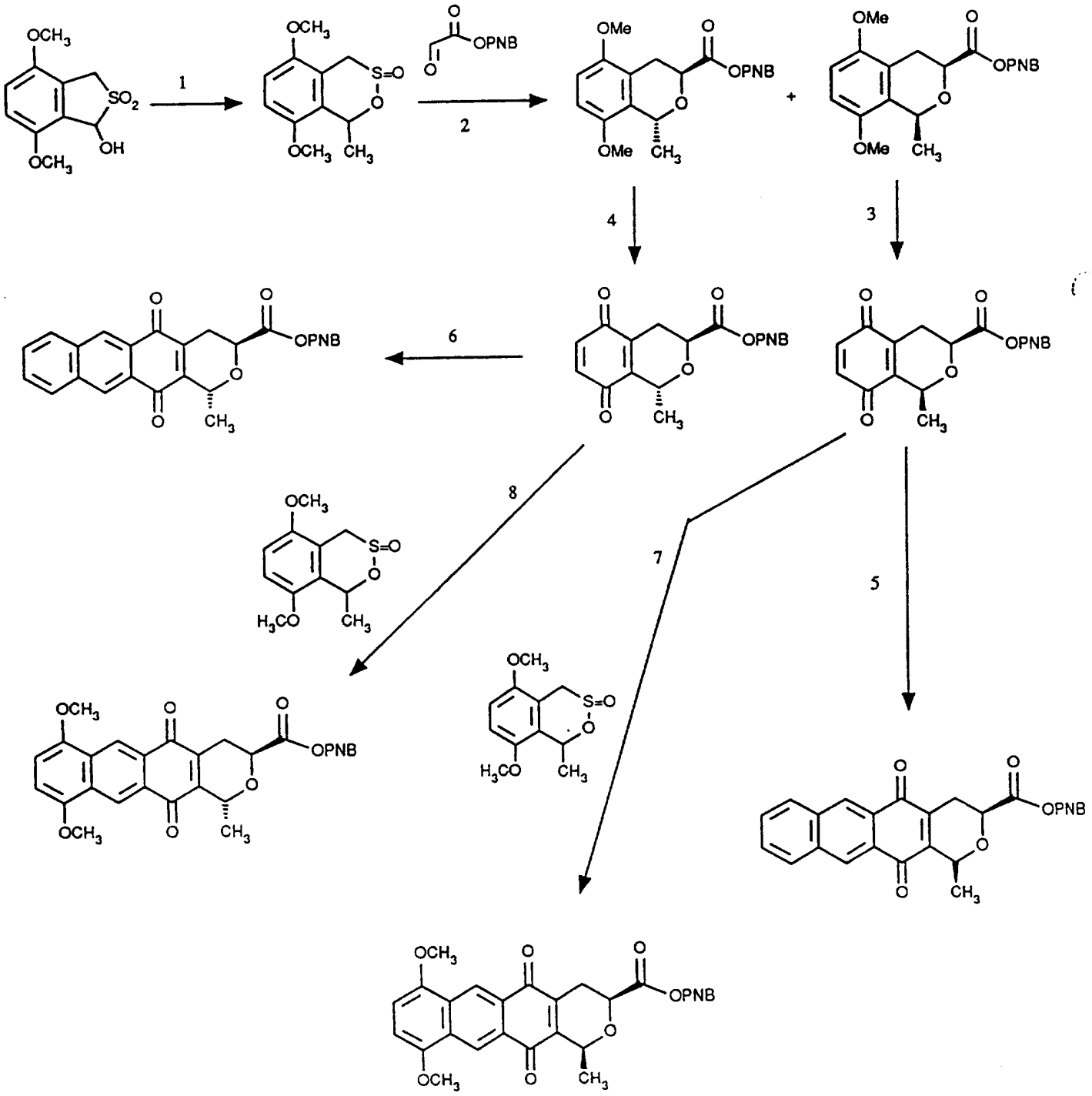
<u>Step 7:</u> (1R,3R) and (1S,3S) Cis-p-nitrobenzyl(5,12-dioxo-7,10-dimethoxy-1-methyl- 3,4,5,12-tetrahydroanthraceno[2,3-c]pyran-3-yl)formate

Following the procedure as described in "example 4, step 2", the reaction between 95 mg (0.4 mmol) of the sultine from example 1, step 4, with 71 mg (0.2 mmol) of the quinone from step 3 above gave 42 mg (41% yield) of the titled tetracycle. (MP: 154°-156°C). ^1H NMR (200 MHz, $CDCl_3$) δ:1.68 (d, 3H, J=7.6 Hz, CH_3), 2.75 (ddd, 1H, J=3.6, 10.7, 18.6 Hz, CH<u>Ha</u>), 3.27 (bdt, 1H, J=2.8, 18.6 Hz, HC<u>He</u>), 4.00 (s, 3H, OCH_3), 4.01 (s, 3H, OCH_3), 4.28 (dd, 1H, J=2.8, 10.7 Hz, OCH), 5.06 (m, 1H, OC<u>H</u>CH_3), 5.38 (bs, 2H, OCH_2), 6.90 (s, 2H, ArH), 7.59 (d, 2H, J=8.9 Hz, ArH), 8.26 (d, 2H, J=8.9 Hz, ArH), 8.95 (s, 1H, ArH), 8.98 (s, 1H, ArH). IR (FT, $CDCl_3$) νmax: 1757, este C=O; 1664, quinone C=O. MS (DCI, 240, NH_3) m/e: 517 (100, M+), 382 (68, $M^+ \cdot - C_7H_5NO_2$).

<u>Step 8:</u> (1R,3R) and (1R,3S) Trans-p-nitrobenzyl(5,12-dioxo-7,10-dimethoxy-1-methyl-3,4,5,12-tetrahydroanthraceno[2,3-c] pyran-3-yl)formate

Following the same procedure as described in "example 4, step 2", the reaction between 70 mg (0.3 mmol) of the sultine from "example 1, step 4", and 53 mg (0.15 mmol) of quinone from step 4 above gave 30 mg (44% yield) of the titled tetracycle. (MP: 180°-182°C). ^1H NMR (200 MHz,

Example 5: Preparation of 1-methylated tetrahydroanthraceno [2,3-c] pyran-3-yl derivatives



$CDCl_3$) δ: 1.57 (d, 3H, J=6.8 Hz, CH_3), 2.84 (ddd, 1H, J=2.1, 9.1, 19.0 Hz, HCHa), 3.06 (ddd, 1H, J=1.2, 4.6, 18.9 Hz, HCHe), 3.95 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.63 (dd, 1H, J=4.69, 8.9 Hz, OCH), 5.29 (m, 1H, $OCHCH_3$), 5.30 (bs, 2H, OCH_2), 6.86 (s, 2H, ArH), 7.50 (d, 2H, J=8.8 Hz, ArH), 8.16 (d, 1H, J=8.8 Hz, ArH), 8.91 (s, 1H, ArH), 8.92 (s, 1H, ArH). CMR (75.44 MHz, $CDCl_3$) δ: 19.7, CH_3; 25.4, CH_2; 55.9, $2XOCH_3$; 65.5, OCH_2; 67.1, 67.8, OCH; 107.6, 123.4, 123.9, 128.7, aryl CH; 127.4, 127.5, 128.6, 140.9, 142.3, 146.8, 150.9, aryl C; 170.4, ester C=O; 182.8, 182.9, quinone C=O. IR (FT, $CDCl_3$) νmax: 1757, ester C=O; 1664, quinone C=O.

EXAMPLE 6

Step 1: 5,8-dimethoxyisochroman-3-yl carboxylic acid

A solution containing 133 mg (0.5 mmol) of the ethylbenzyl-isochroman formate from "example 1, step 5", in 10 ml of THF was added 10 ml of a 1M aqueous sodium hydroxide solution. After stirring at room temperature for 0.5 hour, the mixture was evaporated down to 5 ml and then diluted with 25 ml of water. The aqueous layer was extracted three times with 20 ml aliquots of CH_2Cl_2, then acidified with concentrated aqueous HCl and reextracted four times with 50 ml of ethyl acetate. Only the combined ethyl acetate layers were kept, and after washing twice with water, evaporation of solvent gave 125 mg (99% yield) of the titled isochromanyl acid. (MP: 217-218°C). ^1H NMR (200 MHz, DMSO-d_6) δ: 2.88 (broad ddt, 1H, J=9.9, 17 Hz, HCHaCH), 3.15 (ddd, 1H, J=1.4, 4.6, 17 Hz, HCHeCH), 3.91 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 4.46 (dd, 1H, J=4.5, 9.9, OCHC=O), 4.75 (broad dt, 1H, J=16.4 Hz, ArH, CHaO), 5.05 (broad dd, 1H, J=16.5 Hz, ArHCHeO), 6.92 (dd, 2H, J=11.2 Hz, ArH). CMR (75.44 MHz, $CDCl_3$) δ:26.7, CH_2; 49.9, OCH_2; 55.9, 56.1, $ArOCH_3$; 65.3, OCH; 108.7, 109.1, aryl CH; 123.1, 124.5, 150.6, 152.3, aryl CH; 210.2, CO_2H.

Step 2: Methyl (5,8-dimethoxyisochroman-3-yl) ketone

To a solution containing 150 mg (6.3 mmol) of isochromanyl acid (261) in 15 ml of anhydrous THF was added dropwise, over 5 minutes at -78°C and under argon, 0.94 ml of a 1.4M methyl lithium in ether solution. The solution was stirred for 10 minutes at -78°C then warmed to room temperature and stirred for two more hours. Methanol (1 ml) was then added, followed with 25 ml of water, and the mixture was extracted three times with 50 ml of dichloromethane. The combined organic layer was washed with 25 ml water, 25 ml of saturated aqueous NaCl, and dried over $MgSO_4$. After evaporation of solvent, flash chromatography of the residue (10% ethylacetate in toluene) gave 110 mg (74%) of the titled isochroman ketone. (MP: 84°-85°C). ^1H NMR (200 MHz, $CHCl_3$) δ:2.32 (s, 3H, $COCH_3$), 2.59 (bdd, 1H, J=11.3, 17.00Hz, HCHa), 3.04 (ddd, 1H, J=1.5, 3.8, 17.1, HCHe), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.08 (dd, 1H, J=3.8, 11.4 Hz, O-CH), 4.66 (bd, 1H, J=15.9 Hz, HcHa-O), 5.04 (bd, 1H, J=15.9 Hz, HCHe-O), 6.66 (dd, 2H, J=9.0 Hz, ArH). CMR (75.44 MHz, $CDCl_3$) δ:24.7, CH_2; 25.9, CH_3; 55.4, 55.6, $ArOCH_3$; 64.7, OCH_2; 79.1, OCH; 107.2, 107.7, aryl CH; 122.2, 123.9, 149.2, 151.0, aryl C; 208.4, C=O. IR ($CDCl_3$) νmax: 1717, C=O.

Step 3: Methyl (5,8-dioxo-5,8-dihydroisochroman-3-yl) ketone

To a stirred solution containing 700 mg (3 mmol) of the isochroman from step 2 above in 20 ml of acetonitrile was added dropwise over 5 minutes, at room temperature, a solution containing 2.0g (3.6 mmol) of ceric ammonium nitrate in 20 ml of water. Stirring was continued for five minutes and then 100 ml of dichloromethane was added to the mixture. Successive washings of the organic layer were done with 50 ml of water and 50 ml of brine. After drying

over $MgSO_4$, evaporation of solvent gave 560 mg (92% yield) of the yellow isochromandione, as a dark yellow oil. ^1H NMR (300 MHz, $CDCl_3$) δ:2.34 (s, 3H, $COCH_3$), 2.48 (dddd, 1H, J=2.8, 4.0, 10.1, 19.2 Hz, HCHa), 2.87 (dm, 1H, J=19.2 Hz, HCHe), 4.06 (dd, 1H, J=4.0, 10.1 Hz, OCH), 4.52 (dt, 1H, J=3.3, 18.6 Hz, HCHa-O), 4.83 (ddd, 1H, J=1.0, 2.7, 18.6 Hz, HCHe-O), 6.80 (dd, 2H, J=10.2 Hz, HC=CH). CMR (75.44 MHz, $CDCl_3$) δ: 23.1, CH_2; 25.8, CH_3; 62.7, OCH_2; 77.7, OCH; 136.0, 136.4, CH; 183.3, 139.6, quaternary C; 185.17, 185.24, quinone C=O, 206.4, $COCH_3$. IR ($CDCl_3$) νmax: 1722, $COCH_3$; 1659, quinone C=0.

Step 4: **Methyl(11-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthra- ceno[2,3-c]pyran-3-yl)ketone and Methyl (5-hydroxy-5, 12-dioxo-3,4,5,12-tetrahydroanthraceno[2,3-c]pyran-3- yl)ketone, BCH-687**

These compounds were obtained by following the same procedure as described in step 1 of example 3 and using the methyl 5,8-dimethoxyisochroman-3-yl ketone in this example. Flash chromatography of the residue gave a mixture of both regioisomers (64%) which were not necessarily separated for the next step. The two regioisomers could however, be separated by preparative HPLC. The less polar regioisomer had ^1H NMR (300 MHz, $CDCl_3$) δ: (s, 3H, CH_3), 2.62 (m, 1H, $HCH_2CHC=O$), 3.08 (m, 1H, HCHaCHC=O), 4.10 (dd, 1H, J=10.0, 3.7 Hz, HCHa-O), 5.02 (broad d, 1H, HCHe-O), 7.73 (m, 2H, ArH), 7.97 (m, 1H, ArH), 8.12 (s, 1H, ArH), 8.50 (m, 1H, ArH), 13.86 (s, 1H, ArOH). The more polar regioisomer had ^1H NMR (300 MHz, $CDCl_3$) δ: 2.35 (s, 3H, CF_3), 2.59 (m, 1H, HCHeCHCO), 3.05 (broad dt, J=19.0, 2.8 Hz, HCHaCHCO), 4.08 (dd, 1H, J=10.0, 3.9 Hz, CH), 4.44 (dt, 1H, J=22.5, 6.7, 3.3 Hz, HCHa-O), 5.03 (broad d, 1H, J=18.7 Hz, HCHe-O), 7.71 (m, 2H, ArH), 7.95 (m, 1H, ArH), 8.13 (s, 1H, ArH), 8.46 (m, 1H, ArH), 13.70 (s, 1H, ArOH).

The autoxidized product, methyl (5,12-dihydroxy-6,11-dioxo-3,4,6,11-tetrahydroanthraceno [2,3-c] pyran-3-yl) ketone BCH-688, was also obtained in 8% yield. (MP. 210°C decomposes). ^{1}H NMR (300 MHz, $CDCl_3$, $CDCl_3$) δ: 2.40 (s, 3H, $COCH_3$), 2.81 (m, 1H, HCHa), 3.22 (ddd, 1H, J=2.0, 4.0, 18.1 Hz, HCHe), 4.15 (dd, 1H, J=3.9, 10.6 Hz, OCH), 4.79 (dt, 1H, J=2.2, 17.4 Hz, OHCHa), 5.20 (dd, 1H, J=1.1, 17.4 Hz, HCHe), 7.84 (m, 2H, ArH), 8.36 (m, 2H, ArH), 13.18 (s, 1H, ArOH), 13.31 (s, 1H, ArOH).

Step 5: **Methyl(6,11-diacetoxy-5,12-dioxo-3,4,5,12-tetrahydroan-thraceno[2,3-c]pyran-3-yl)ketone**

The titled compound was obtained in 45% yield by following the same procedure as described in example 3 by sequentially carrying out step 7 and 8. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.35 (s, 3H, $COCH_3$), 2.51 (s, 3H, $OCOCH_3$), 2.54 (s, 3H, $OCOCH_3$), 2.72 (m, 1H, HCHa), 3.05 (m, 1H, HCHe), 4.08 (m, 1H, OCHC=O), 4.73 (bd, 1H, OHCHa), 5.08 (bd, 1H, OHCHe), 7.65 (m, 2H, ArH), 8.15 (m, 2H, ArH).

The mixture of monoacetoxylated compounds BCH-721 methyl (6-hydroxy-11-acetoxy and 6-acetoxy-11-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl) ketone, could be recovered in 10%.

Step 6: **Methyl (11-acetoxy-1,6-dihydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno[2,3-c]pyran-3-yl)ketone.**

The titled compound was obtained in 24% yield by following the same procedure as described in example 3, step 9. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.38 (s, 3H, $COCH_3$), 2.52 (s, 3H, $OCOCH_3$), 3.04 (m, 2H, CH_2), 4.55 (m, 1H,

OCHC=O), 6.36 (bs, 1H, OCHOH), 7.82 (m, 2H, ArH), 8.23 (m, 2H, ArH).

Step 7: (1'S,1R,3S) and (1'S,1S,3R) Methyl (1-[2',3',6'-trideoxy-3'-trifluoroacetamido-L-4'-O-p-nitrobenzoyl-L-lyxohexo-pyranose)-6-hydroxy-11-acetoxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno(2,3-c)pyran-3-yl)ketone

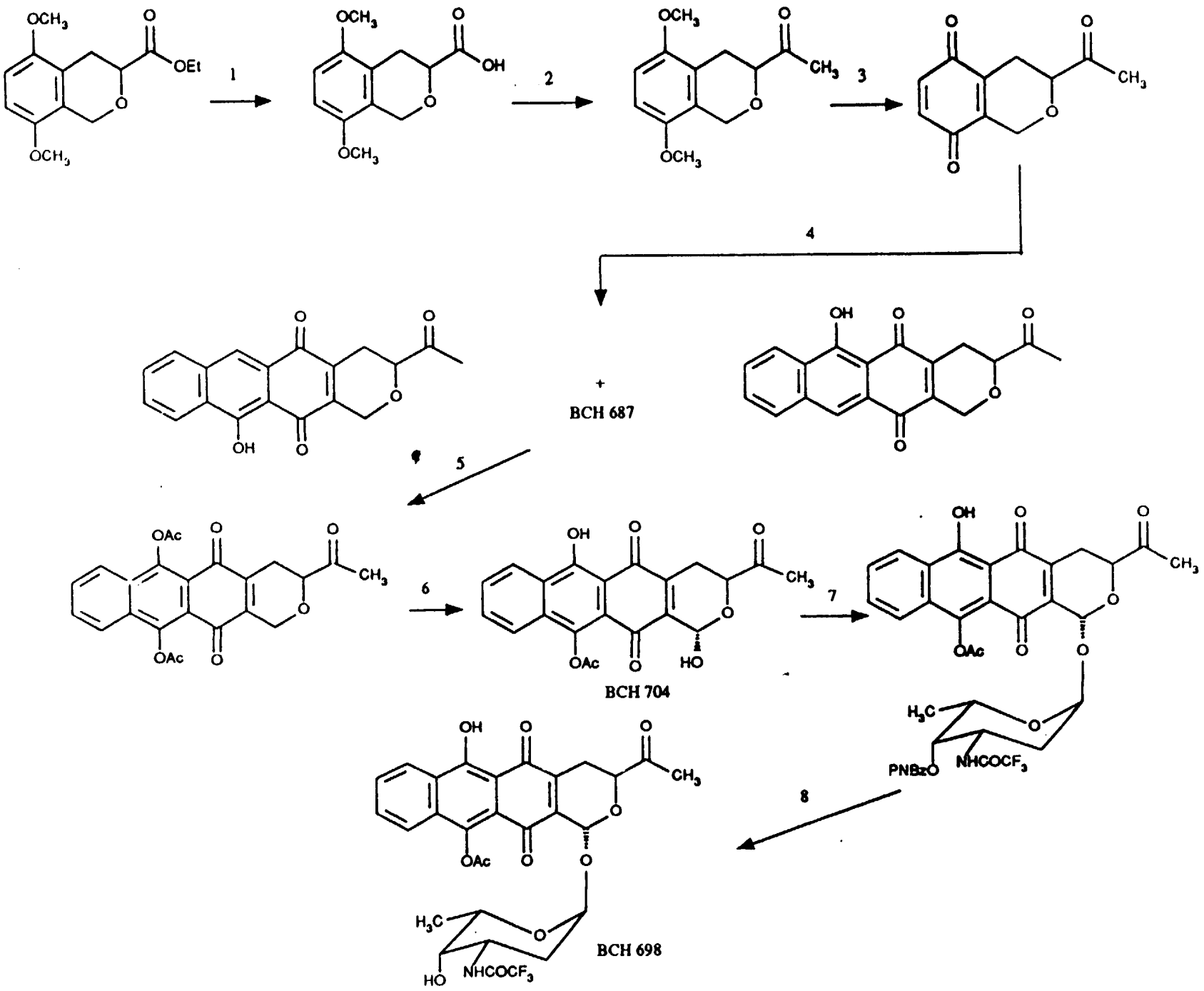
Following the regular glycosylation procedure (step 10, example 1) the desired titled pyranoanthracycline gycoside 2 were obtained in 37% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (overlapped d, 3H, 6'-CH_3), 2.11 (m, 2H, 2'-CH_2), 2.38 (s, 3H, -$COCH_3$), 2.53 (s, 3H, -$OCOCH_3$), 2.68 (m, 1H, HCHa), 3.21 (m, 1H, HCHe), 4.39 (m, 1H, 5'-CH), 4.63 (m, 2H, 3' and 4' CH), 5.16 (dd, 1H, J=4.1, 12.6 Hz, O-CH), 5.48 and 5.78 (bs, 1H, 1'-CH), 6.21 (s, 1H, O-CH-O), 7.81 (m, 2H, ArH), 8.25 (overlapped m, 6H, ArH), 13.69 (s, 1H, ArOH).

Step 8: (1'S')Methyl[1-(N-trifluoroacyldaunosamine)-6-hydroxy-11-acetoxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno(2,3-C)pyran-3-yl]ketone.

A cooled (-5°C) solution containing 48.4 mg (0.06 mmol) of the glycoside from step (before) in 5 ml of dichloromethane was treated with 5 ml of a 0.2 M NaOH methanolic solution for 15 minutes. The reaction mixture was then quenched by acidification with 0.1N HCl to pH 6, extracted with CH_2Cl_2 (2x15 ml) and the combined organic phases were washed with water (2x30 ml) and dried (Na_2SO_4). Purification by HPLC (spherex CN5U; hexane; ethylacetate; 80%-20%) gave 5.3 mg (14% yield) of the desired compound. (MP. 235-236°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.30 (d, 3H, J=6.7 Hz, CH_3), 1.87 (m, 1H, 2'- HCHa), 2.12 (m, 1H, 2'-HCHe), 2.37 (s, 3H, -

$COCH_3$), 2.53 (s, 3H, $OCOCH_3$), 2.62 (m, 1H, HCHa), 3.14 (m, 1H, HCHe), 3.63 (bs, 1H, 4'-CH), 4.17 (bq, 1H, J=6.7 Hz, 5'-CH), 4.39 (m, 1H, 3'-CH), 4.60 (dd, 1H, J-3.6, 11.4, O-CH), 5.57 (bs, 1H, 1'-CH), 6.13 (s, 1H, O-CH-O), 6.67 (bd, 1H, J-8.4 Hz, NH), 7.79 (m, 2H, ArH), 8.21 (m, 1H, ArH), 8.29 (m, 1H ArH), 13.49 (s, 1H, ArOH).

Example 6 : Preparation of tetrahydroanthraceno [2,3-c] pyran-3-yl derivatives with a methyl ketone substituent



EXAMPLE 7

Step 1: 3-formyl-5,8-dimethoxyisochroman

Ethyl-(5,8-dimethoxyisochroman-3-yl) formate (697 mg, 2.62 mmol) was dissolved in toluene (20 ml) and cooled to -78°C. DIBAL (2.97 ml, 1.5M, 4.45 mmol) was cooled to -78°C and added slowly to the reaction mixture over a period of 15-20 minutes. A TLC taken right away after the addition revealed that the reaction was over. Cold MeOH (4 ml) was added slowly (H_2 evolution!) and the mixture was extracted with ethyl acetate (3x50 ml). The organic phases were combined, washed with brine and dried over $MgSO_4$. Flash chromatography of the crude residue gave the title products (483 mg, 83%). ^1H NMR (300 MHz, $CDCl_3$) δ:2.63 (dd, 1H, J=16.8, 11.3 Hz, HC<u>Ha</u>CHC=O), 2.99 (dd, 1H, J=17.0, 3.8 Hz, HC<u>He</u>CHC=O), 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.09 (dd, 1H, J=10.7, 4.4 Hz, He=O), 4.87 (dd, 2H, J=103.8, 15.9 Hz, HC<u>Ha,e</u>-O), 6.66 (m, 2H, ArH).

Step 2: 3-(1-hydroxy-2-methoxymethoxy)ethyl-5,8-dimethoxyiso- chroman

A solution of nBu_3SnCH_2OMOM (1,066g, 2.92 mmol) in 12 ml of THF was cooled to -78°C under argon. The solution was stirred while n-BuLi (1,1 ml, 2.5M, 2.75 mmol) was added. After 30 minutes, 3-formyl-5,8-dimethoxyisochroman (483 mg, 2.18 mmol) was added. After 45 minutes, the cold reaction mixture was partitioned between water and ether. The organic phase was dried over $MgSO_4$, filtered, and concentrated. Flash chromatography of the crude residue (hexane/ethyl acetate; 1:1) gave the title compound in 66% yield (431 mg). The following spectral data were obtained from the mixture of two diastereoisomers. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: From 2.49 to 3.10 (m, 3H, HC<u>Ha,e</u>-CH-C-O and OH), 3.35 (s, 3H, $CH_2OC\underline{H}_3$), from 3.55 to 3.92 (m, 6H, $C\underline{H}_2$-

OMe, CHaeCH=O and CH-OH), 3.69 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 4.55 (m, 1H, HCHa-O), 4.64 (s, 2H, OCH_2-OCH_3), 4.90 (m, 1H, HCHe-O), 6.57 (m, 2H, ArH). IR: [illegible], 3464 (OH), 2930, 2830, 1480, cm^{-1}.

Step 3: 5,8-dimethoxy-3-(methoxymeth[illegible]ochroman

To a stirred solution of oxalyl [illegible] 3.37 ml, 38.67 mmol) in 80 ml of CH_2Cl_2 was [illegible]ropwise a solution of DMSO (2.99 ml, 38.67 mmol [illegible] of CH_2Cl_2 at -78°C under argon over a period [illegible]utes. The stirring was continued for 15 minu[illegible] a solution of 3-(1-hydroxy-2-meth[illegible] dimethoxyisochroman (3,842g, 12.89 mmol [illegible] over a period of 5 min[illegible]s. [illegible] for 45 minutes at -[illegible]C, [illegible] introduced. The rea[illegible] temperature over 1 ho[illegible] The aqueous layer was [illegible] the combined organic phases [illegible] brine, dried over $MgSO_4$, filt[illegible] yellow residue that was purif[illegible]y [illegible]phy (hexane/ethyl acetate; 7:3) to [illegible]nds (3.295g, 86%). ^1H NMR (300 MH[illegible] 1H, J=13.9, 5.7 Hz, HCHaCHC=O), 3.0[illegible] 3.39 (s, 3H, CH_2OCH_3), 3.75 (s, 3H, [illegible]H_3), [illegible]H_3), 4.19 (dd, 1H, J=11.4, 3.8 Hz, CH-O), [illegible]H_3), 4.79 (dd, 2H, J=111.[illegible] 15.9 Hz), 6.6[illegible] ^{13}C NMR (75.44 MHz, CDCl[illegible]; δ: [illegible].37, 5[illegible] [illegible].31, 71.21, 97.06, 107.84, [illegible] 122.[illegible] [illegible].81, 151.62, 206.78. IR (neat) [illegible], 1580, 1510, 1480 cm^{-1}.

Step 4: 3-(methoxymethoxy)aceto-5,8-dioxo[illegible]chroman

5,8-dimethoxy-3-(methoxymethoxy)-acetoisochroman

(3.155g, 10.59 mmol) was dissolved in acetonitrile (35 ml) and cooled to 0°C. A solution of ceric ammonium nitrate (CAN) (17.53g in 35 ml of H_2O) was added dropwise with stirring. The ice bath was then removed and stirred for an extra 15 minutes. Water (30 ml) was added and the mixture was extracted with CH_2Cl_2. The organic phases were washed with water, dried over $MgSO_4$, filtered and concentrated in vacuo to give a reddish oil which was found to be pure title compound without flash chromatography. (2.38g, 85% yield). ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 2.52 (m, 1H, HCHa-CHC=O), 2.90 (m, 1H, HCHeCHC=O), 3.39 (s, 3H, OCH_2OCH_3), 4.19 (dd, 1H, J=10.3, 3.8 Hz, HC-O), 4.44 (td, 1H, J=18.7, 3.7 Hz, HCHa-O), 4.54 (s, 2H, OCH_2-OCH_3), 4.70 (s, 3H, $COCH_2$-OMOM), 4.77 (dd, 1H, J=18.6, 2.5 Hz, HCHe-O), 6.75 (m, 2H, ArH).

Step 5: 3-(2-methoxymethoxy)aceto-6-hydroxy-1,2,3,4-tetrahydro-(2-oxygen)napthacene-5,12-dione and 3-(2-methoxymethoxy)aceto-11-hydroxy-1,2,3,4-tetrahydro-(2-oxygen)-napthacene-5,12-dione

To a solution of LDA (9.42 mmol) in 30 ml of THF was added dropwise a solution of homophthalic anhydride (1.53g, 9.43 mmol) in 30 ml of THF at -78°C under argon. After 5 minutes, a solution of 3-(2-methoxymethoxy)aceto-5,8-dioxoisochroman (2.3589, 8.14 mmol) in 35 ml of THF was introduced. The stirring was continued at -78°C for 20 minutes and then at room temperature for 30 minutes. After the mixture was kept in the fridge overnight, it was quenched with sat. NH_4Cl solution (40 ml) and then carefully partitioned between 1N HCl (15 ml) and CH_2Cl_2 (150 ml). The organic layer was washed with brine, dried over Na_2SO_4, and then concentrated to a crude residue which was purified by flash chromatography to give a mixture of the two regioisomers (46%). The following spectral data were obtained from the mixture of two regioisomers. ^1H NMR

(300 MHz, $CDCl_3$), δ:2.58 (m, 2H, HC<u>Ha</u>CHC=O), 3.04 (dd, 2H, J=19.2, 3.26 Hz, HC<u>He</u>-CHCO), 3.40 (s, 6H, OCH_3), 4.22 (m, 2H, CH-O), 4.57 (s, 4H, $OC\underline{H}_2OCH_3$), 457 (m, 2H, HC<u>Ha</u>-O), 4.58 (s, 4H, $COC\underline{H}_2$-OMOM), 4.87 (m, 2H, HC<u>He</u>-O, 7.67 (m, 4H, ArH), 7.69 (m, 2H, ArH), 7.86 (m, 2H, ArH), 8.38 (m, 2H, ArH). IR: (neat) 2925, 2843, 1740 (CO), 1654, 1639, 1608, 1568 cm^{-1}.

<u>Step 6:</u> 6 and 11-acetoxy-3-(2-methoxymethoxy)aceto-1,2,3,4-tetrahydro-(2-oxygen)naphtacene-5,12-dione

The regioisomeric mixture from step 5 above (1,962g, 5.13 mmol) was dissolved in CH_2Cl_2 (130 ml). Acetic anhydride (26.7 ml), pyridine (26.7 ml) and DMAP (0,518g) were successively added and stirred at room temperature for 30 minutes. The reaction mixture was then poured onto ice water, and extracted with CH_2Cl_2. The organic layers were combined, washed with HCl (4%), water, dried over sodium sulfate, and concentrated to give a crude residue which was flash chromatographed using hexane/EtOAc (1:1) to give a mixture of the desired titled compounds in greater than 80% yield. The following spectral data were obtained from the two regioisomeric mixtures. ^1H NMR (300 MHz, $CDCl_3$), δ:2.54 (m, 2H, HC<u>Ha</u>CHC=O), 3.10 (m, 2H, HC<u>He</u>CHC=O), 3.40 (s, 3H, $CH_2OC\underline{H}_3$), 3.41 (s, 3H, $CH_2OC\underline{H}_3$), 4.23 (dd, 2H, J=10.48, 3.84 Hz, OCHC=O), 4.58 (s, 2H, CO-$C\underline{H}_2$OMOM), 4.58 (s, 2H, $COC\underline{H}_2$OMOM), 4.58 (m, 2H, HC<u>Ha</u>-O), 4.72 (s, 4H, $COC\underline{H}_2OCH_3$), 4.95 (m, 2H, HC<u>He</u>-O), 7.72 (m, 4H, ArH), 8.19 (m, 4H, ArH), 8.54 (s, 1H, ArH), 8.58 (s, 1H, ArH).

Step 7: 3-(2-hydroxy-1-propyleneketal)aceto-6-acetoxy-1,2,3,4-tetrahydro-(2-oxygen)naphtacene-5,12-dione and
3-(2-hydroxy-1-propyleneketal)-aceto-11-acetoxy-1,2,3,4-tetrahydro-(2-oxygen)naphtacene-5,12-dione

The mixture of tetracycles from step 6 above (70 mg, 0.16 mmol) was dissolved in toluene (30 ml) followed by the addition of 1,3-propanediol (1 ml) and PPTS (2 mg). The reaction mixture was refluxed overnight using a Dean Stark trap to remove the water formed during the process. The reaction mixture was extracted with CH_2Cl_2, the organic phases were combined, washed with H_2O, dried over sodium sulfate, and concentrated in vacuo. The crude residue obtained was flash chromatographed using EtOAc/CH_2Cl_2 (1:1) to give the desired title products (66 mg) in 94% yield. The following spectral data were recorded on the two regioisomeric mixtures. ^1H NMR (300 MHz, $CDCl_3$) δ:1.55 (m, 2H, O-CH_2-CH-H-CH_2-O), 1.85 (m, 2H, O-CH_2-CH-H-CH_2-O), 2.05 (m, 2H, OH), 2.25 (m, 2H, HCHaCHC<), 2.58 (s, 3H, $OCOCH_3$), 2.61 (s, 3H, $OCOCH_3$), 2.80 (m, 2H, HCHeCHC<), from 3.55 to 4.15 (m, 14H, O-CH_2-CH_2-O, CH_2OH and HC-O), 4.52 (m, 2H, HCHa-O), 4.94 (m, 2H, HCHe-O), 7.69 (m, 4H, ArH), 8.07 (m, 4H, ArH), 8.52 (s, 1H, ArH), 8.57 (s, 1H, ArH). IR: (neat) 3454.6, 2929.2, 2878.6, 1766.4 (CO), 1658.0, 1612.4 cm^{-1}.

Step 8: 3-(2-acetoxy-1-propyleneketal)aceto-6-acetoxy-001,2,3,4-tetrahydro-(2-oxygen)naphtacene-5,12-dione and
3-(2-acetoxy-1-propyleneketal)aceto-11-acetoxy-1,2,3,4-tetrahydro-(2-oxygen)naphtacene-5,12-dione

A mixture of tetracyclic compounds of step 7 above (367 mg, 0.84 mmol) was dissolved in CH_2Cl_2 (20 ml)

followed by the successive addition of acetic anhydride (1,0 ml), pyridine (1,0 ml) and DMAP (60.9 mg). Within half hour, the reaction was complete. It was extracted with CH_2Cl_2. The organic phases combined, washed with H_2O, dried over $MgSO_4$, and concentrated in vacuo. The crude residue obtained was flash chromatographed using hexane/EtOAc (7:3) to give the desired products as a mixture (278 mg, 0.6 mmol, 69%). The following spectral data were recorded on the two regioisomeric mixtures. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ:1.85 (m, 4H, OCH_2CH_2-CH_2O), 2.11 (s, 6H, CH_3OCOCH_3), 2.60 (s, 3H, $OCOCH_3$), 2.63 (s, 3H, $OCOCH_3$), 2.86 (m, 4H, HCHa-CHC<) 3.98 (m, 10H, OCH_2CH_2-CH_2-O and OCHC<), 4.29 (d, 2H, J=11.87, CH_2-$OCOCH_3$), 4,5 (m, 2H, HCHa-O), 4.94 (dd, 2H, HCHaO), 5.05 (d, 2H, CH_2OCOCH_3), 7.70 (m, 4H, ArH), 8.10 (m, 4H, ArH), 8.56 (s, 1H, ArH), 8.61 (s, 1H, ArH), IR: (neat) 2922.3, 1774.8, 1745.6 (C=O), 1669.9, 1617.5 (C=O quinone), 1431.1 cm^{-1}.

Step 9: 3-(2-acetoxy-1-propyleneketal)aceto-6-acetoxy-1-hydroxy-1,2,3,4-tetrahydro-(2-oxygen)naphtacene-5,12-dione and 3-(2-acetoxy-1-propyleneketal)-aceto-11-acetoxy-1-hydroxy-1,2,3,4-tetrahydro-(2-oxygen)naphtacene-5,12-dione

A mixture of tetracyclic compounds of step 8 above (34 mg, 0.09 mmol) was dissolved in CCl_4 (13 ml) followed by addition of NBS (32 mg, 0.18 mmol) and benzoyl peroxide (2 mg). The reaction mixture was refluxed and irradiated by sun-lamp under argon for about one hour. It was then concentrated in vacuo and treated with stirred in THF/H_2O (6 ml, 1:1) before it was extracted with CH_2Cl_2. The organic phases were combined, washed with H_2O, dried over sodium sulfate and concentrated in vacuo. The crude residue obtained was flash chromatographed using

EtOAc/CH_2Cl_2 (1:1) to give the desired products as a mixture (26.5 mg, 0.05 mmol, 59%). The following spectral data were recorded on the two regioisomeric mixtures. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ: 1.85 (m, 4H, OCH_2-C<u>H_2</u>-CH_2-O), 2.12 (s, 6H, CH_2OCOC<u>H_3</u>), 2.60 (s, 3H, $OCOC$<u>H_3</u>), 2.62 (s, 3H, $OCOC$<u>H_3</u>), 2.86 (m, 4H, HC<u>Ha,e</u>CHC<), 4.08 (m, 8H, OC<u>H_2</u>-CH_2-C<u>H_2</u>-O), 4.38 (d, 2H, C<u>H_2</u>-$OCOCH_3$), 4.46 (dd, 2H, OCHC<, 4.89 (broad d, 2H, J=12.03, CH_2-$OCOCH_3$), 6.14 (broad d, 2H, J=12.64, C<u>H</u>OH 7.71 (m, 4H, ArH), 8.05 (m, 4H, ArH), 8.56 (s, 1H, ArH), 8.59 (s, 1H, ArH). IR: (neat) 3402.0 (OH), 2925.3, 1772.2; 1735.0, 1666.8, 1617.3, 1443.7 cm^{-1}.

<u>Step 10:</u> 3-(2-hydroxy)aceto-6-hydroxy-1,2,3,4-tetrahydro-(2-oxygen)naphthacene-5,12-dione and 3-(2-hydroxy)aceto-11-hydroxy-1,2,3,4-tetrahydro-(2-oxygen)naphthacene-5,12-dione

A reaction mixture containing both tetracyclic regioisomers from step 5 above (500 mg, 30%, 0.39 mmol) was dissolved in 20 ml of CH_3OH followed by addition of 10 ml of 2.5 HCl solution. The mixture was stirred at room temperature for 0.5h before it was extracted with CH_2Cl_2 (150 ml). The organic layer was washed with H_2O, dried over $MgSO_4$, filtered and then concentrated to a residue that was purified by flash to give an inseparable mixture of the titled compounds. (20 mg, 15%). The following spectra were recorded on the two regioisomeric mixtures. ^1H NMR (300 MHz, $CDCl_3$) δ:2.80 (m, 1H, HC<u>Ha</u>CHC=O), 3.1 (m, 1H, HC<u>He</u>CHC=O), 3.67 (s, 2H, CH_2OH), 3.84 (s, 3H, OCH_3), 4.33 (m, 1H, CH-O), 4.68 (m, 1H, HC<u>Ha</u>O), 5.03 (m, 1H, HC<u>He</u>-O), 7.71 (m, 2H, ArH), 7.94 (m, 1H, ArH), 8.11 (m, 1H, ArH), 8.48 (m, 1H, ArH), 13.70 (s, 1H, exchangeable OH), 13.83 (s, 1H, exchangeable OH).

Step 11: 6,11-diacetoxy-3-(2-methoxymethoxy)aceto-1,2,3,4-tetrahydro-(2-oxygen)naphthacene-5,12-dione

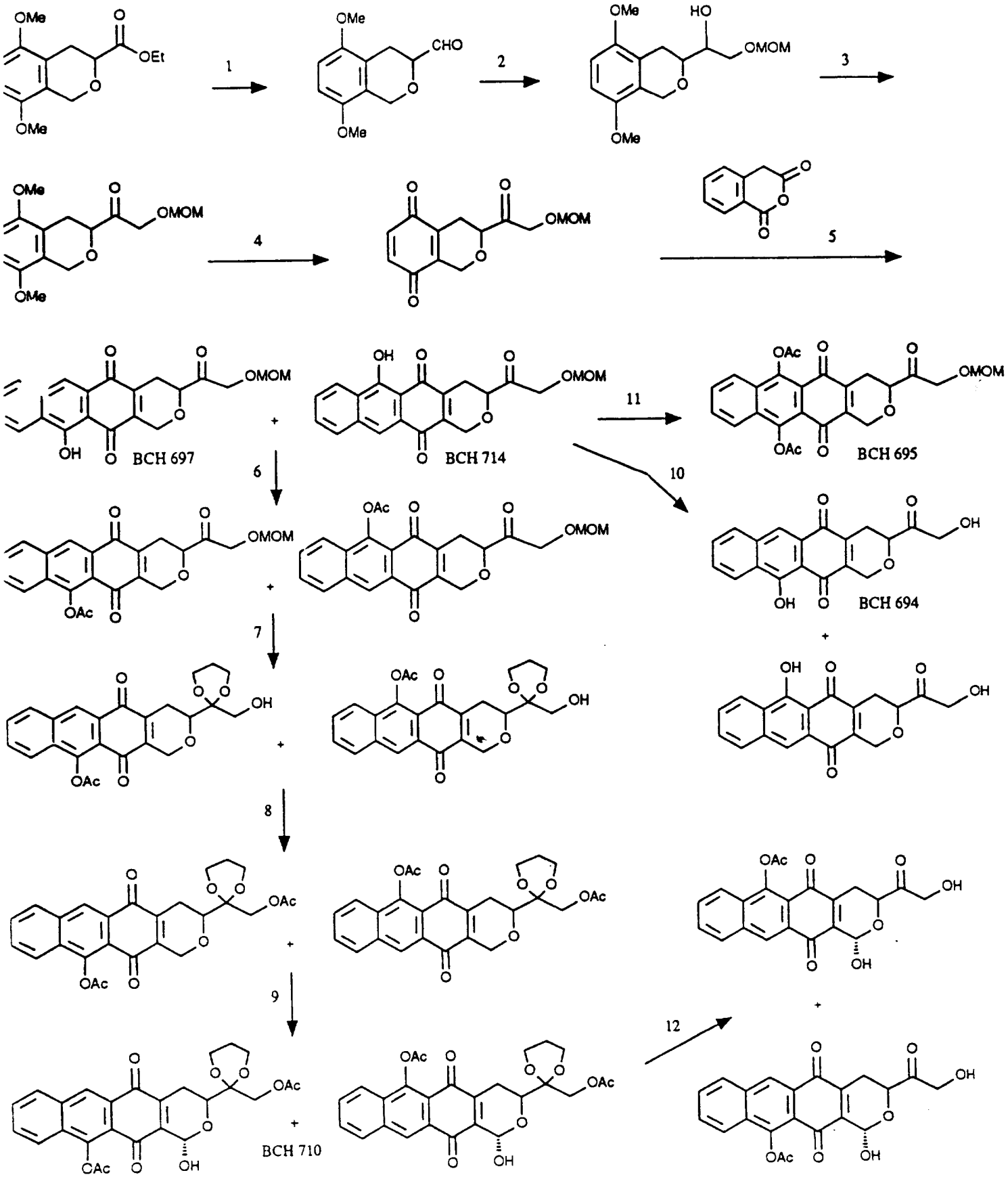
A mixture of tetracyclic compounds from step 5 above (273 mg, 0.71 mmol) was treated with $pb(OAc)_4$ (370 mg, 3.1 mmol) in dark in the presence of 10 ml CH_2Cl_2 and 30 ml AcOH at room temperature for 2 days. The mixture was concentrated in vacuo. The residue was partioned between H_2O and $CHCl_3$. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated to a residue which was then treated with Ac_2O (4 ml), pyridine (4 ml) and DMAP (68 mg) for 2 hours. 20 ml of H_2O and 50 ml of CH_2Cl_2 were added. The organic layer was separated, washed with NaCl solution and dried over $MgSO_4$. Flash chromatography of the residue gave the titled compound (47 mg, 17%). The following spectral data were recorded on the two regiosomeric mixtures. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.50 (s, 3H, $OCOCH_3$), 2.51 (s, 3H, $OCOCH_3$), 2.25 (m, 1H, HCH_aCH-C=O), 3.10 (m, 1H, HCH_eCHC=O), 3.40 (s, 3H, CH_2OCH_3), 4.27 (m, 1H, CHO), 4.61 (s, 2H, CH_2OCH_3), 4.72 (s, 2H, $COCH_2OMOM$), 4.70 (m, 1H, HCH_e-O), 5.05 (m, 1H, HCH_e-O), 7.73 (m, 2H, ArH), 8.16 (m, 2H, ArH). IR: (neat) 2934, 1775, 1742 (CO), 1683, 1598, cm^{-1}.

Step 12: 3-(2-hydroxy)aceto-6-acetoxy-1-hydroxy-1,2,3,4-tetrahydro-(2-oxygen)naphtacene-5,12-dione and 3-(2-hydroxy)aceto-11-acetoxy-1-hydroxy-1,2,3,4-tetrahydro-(2-oxygen)naphtacene-5,12-dione

A mixture of tetracyclic compounds from step 11 above (30 mg, 0.06 mmol) was dissolved in acetone and H_2O (12 ml, 1:1, 58.42) followed by the dropwise addition of HCl conc. (~4 ml). The mixture was stirred at room temperature for

several hours until the starting material was consumed. $NaHCO_3$ solution (sat.) was then added until a pH of 8 was obtained. The mixture was then extracted with CH_2Cl_2, dried over sodium sulfate and concentrated in vacuo. The crude residue obtained was flash chromatographied using ethyl acetate:CH_2Cl_2 (1:1) to give the title compounds as a mixture (9.3 mg, 0.02 mmol, 39%). The following spectral data were obrained from the regioisomeric mixtures. ^1H NMR (300 MHz, $CDCl_3$) δ:2.62 (s, 6H, $OCOCH_3$), 3.15 (m, 2H, HCHaCHC=O), 3.62 (m, 2H, HCHeCHC=O), 4.62 (m, 4H, CH_2OH), 4.88 (m, 2H, CH=O), 6.16 (d, 2H, J=13.95 Hz, CHOH), 7.74 (m, 4H, ArH), 8.11 (m, 4H, ArH), 8.62 (m, 2H, ArH). IR: (neat) 3367.6 (broad, OH), 2932.2, 2855.7, 1771.7, 1738.8 (C=O). 1664.9, 1617.9 (CO, quinone) cm^{-1}.

Example 7: Preparation of tetrahydroanthraceno [2,3-c] pyran-3-yl derivatives with a hydroxymethyl ketone substituent



EXAMPLE 8

Step 1: 3-carbomethoxy-5,8-dimethoxyisothiochroman

1,4-dimethoxy-2,3-dibromomethylbenzene (10.0g, 30.88 mmol) was dissolved in CH_2Cl_2 and MeOH (750 ml, 6:4) followed by addition of ethyl 2-mercaptoacetate (4.02 ml, 37.06 mmol) with stirring under argon. The mixture was then cooled to 0°C followed by dropwise addition of sodium methoxide (4.37M, 8.5 ml, 37.06 mmol) over a period of 2h using an automatic syringe pump. After 5 minutes the solvent was evaporated and the crude was redissolved in THF (400 ml) and cooled to 0°C again. NaOEt (2.10g, 30.88 mmol) was then added. The ice bath was removed and the reaction was stirred for 2 more hours. The reaction mixture was then quenched with NH_4Cl (sat.) and extracted with ether. The organic phases were combined, dried over $MgSO_4$, filtered and concentrated. The crude residue was then treated with NaOME in MeOH and THF at 0°C for 2 hours. The reaction mixture was extracted with ether (100 mlx2). The combined organic phases were washed with H_2O, dried over $MgSO_4$, filtered and concentrated to a residue that was purified by flash chromatography to give title compound in 45% yield. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ:2.97 (dd, 1H, J=16.51, 8.79 Hz, HCHaCHC=O), 3.36 (dd, 1H, J=16.7, 5.1 Hz, HCHeCHC=O), 3.73 (m, 2H, HCHa,e-O), 3.75 (s, 3H, OCH_3), 3.78 (s, 6H, 2xOCH_3), 3.85 (m, 1H, HC-S), 6.69 (m, 2H, ArH).

Step 2: 3-carbomethoxy-5,8-dioxoisothiochroman

To a stirred solution of isothiochroman from step 1 above (253 mg, 0.94 mmol) in 3 ml of CH_3CN was added

dropwise a solution of ceric ammonium nitrate (1.550g, 283 mmol) in 3 ml of H_2O. The reaction mixture was stirred at 0°C for 10 minutes and then at room temperature for 10 minutes, followed by extraction with CH_2Cl_2 (10 mlx3). The combined organic layers were washed with brine and water, dried over $MgSO_4$, and then concentrated to a yellow residue (213 mg, 0.89 mmol) in 95% yield, which was found to be pure by H^1NMR. ^1H NMR (300 MHz, $CDCl_3$) δ:2.90 (m, 2H, HC<u>Ha,e</u>CHC=O), 3.56 (m, 2H, HC<u>Hae</u>-S), 3.73 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 3.75 (m, 1H, HC-S), 6.75 (m, 2H, ArH). ^{13}C NMR (75.44 MHz, $CDCl_3$) δ: 22.2, 26.0, 37.4, 52.8, 136.2, 137.0, 140.0, 140.5, 172.0 (CO ester), 185.8, 187.0 (CO quinones). IR: (neat) 2956, 1736, 1658, 1607, 1442, 1409 cm^{-1}.

<u>Step 3:</u> **3-carbomethoxy-6-hydroxy-1,2,3,4-tetrahydro-(2-sulfur)naphthacene-5,12-dione and 3-carbomethoxy-11-hydroxy-1,2,3,4-tetrahydro(?-sulfur)naphthacene-5,12-dione**

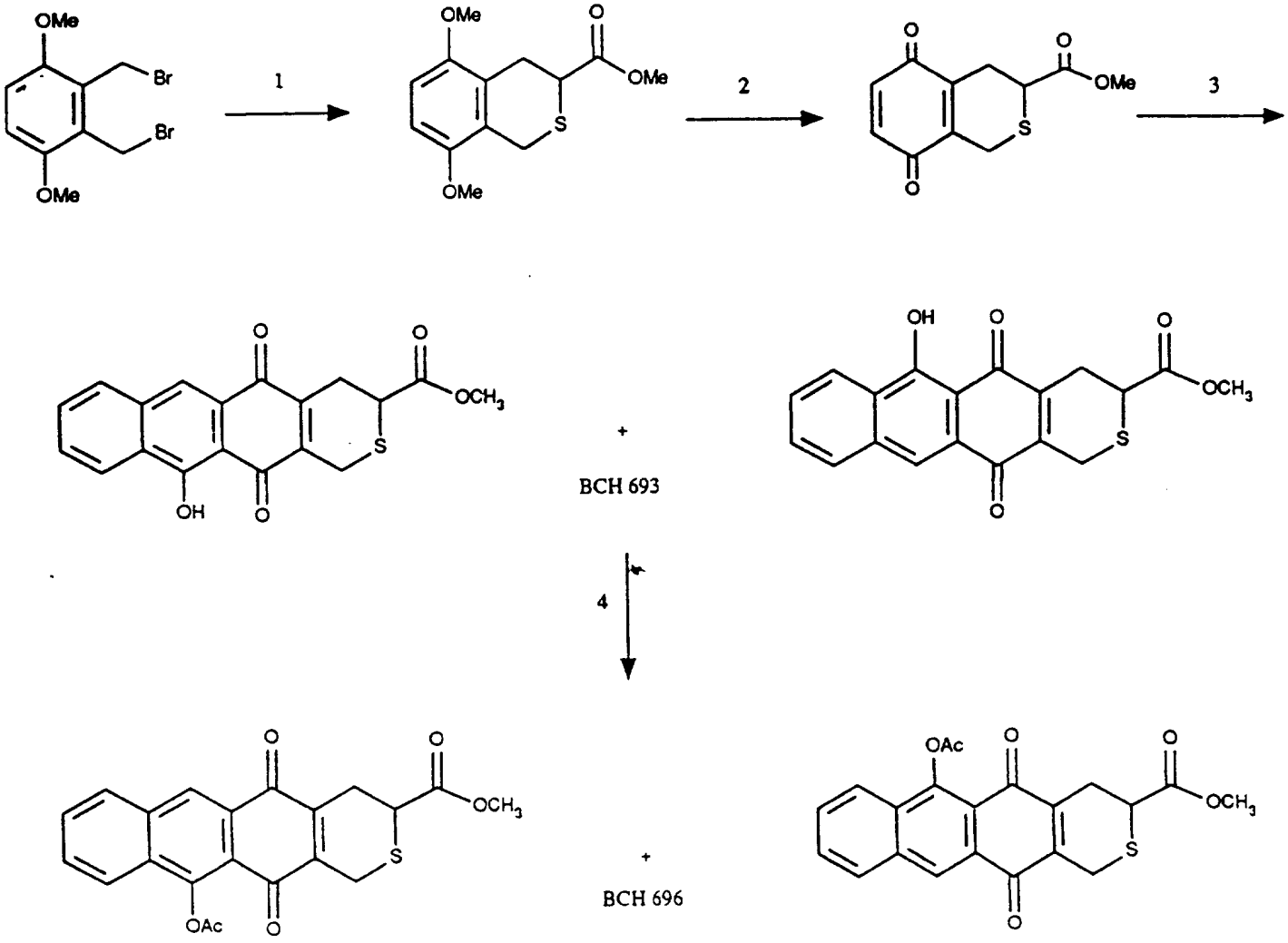
To a stirred solution of LDA (0.98 mmol in 4 ml of THF) was added dropwise a solution of homophthalic anhydride (160.2 mg, 0.99 mmol) in 4 ml of dry THF at -78°C under argon. After stirring for 10 minutes a solution of quinone from step 3 above (213.0 mg, 0.89 mmol) in 4 ml of THF was introduced. The stirring was continued at -78°C for 20 minutes and then at room temperature for 1h. The mixture was quenched with sat. NH_4Cl solution (10 ml) and then partioned between 0.5 N HCl (10 ml) and CH_2Cl_2 (50 ml). The organic layer was washed with brine, dried over Na_2SO_4 and concentrated <u>in vacuo</u>. The residue was purified by flash chromatography with hexane and ethyl acetate (7:3) to give a mixture of titled compounds (125 mg, 40%). The following spectral data were obtained from the two regioisomeric mixtures. ^1H NMR (300 MHz, $CDCl_3$), δ:3.09

(dm, 1H, HC<u>Ha</u>CHC=O), 3.21 (dm, 1H, HC<u>He</u>CHC=O), 3.73 (m, 1H, CHS), 3.76 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.82 (m, 2H, HC<u>Ha,e</u>-O), 7.69 (m, 2H, ArH), 7.71 (m, 1H, ArH), 8.09 (s, 1H, ArH), 8.44 (m, 1H, ArH), 13.80 (s, 1H, exchangeable OH), 13.89 (s, 1H, exchangeable OH).

<u>Step 4:</u> 6-acetoxy-3-carbomethoxy-1,2,3,4-tetrahydro-(2-sulfur) napthacene-5,12-dione and 11-acetoxy-3-carbomethoxy-1,2,3,4-tetrahydro-(2-sulfur) napthacene-5,12-dione

A mixture of tetracycles from step 3 above (95 mg, 0.268 mmol) was treated with Ac_2O (2 ml), pyridine (2 ml) and catalytic amount of DMAP (34 mg) in 10 ml of CH_2Cl_2 at room temperature. After stirring for 0.5h, the mixture was poured into 25 ml of ice water and then diluted with 25 ml of CH_2Cl_2. The organic layer was washed twice with 0.5 N HCl solution (2x20 ml) and then dried over Na_2SO_4. Filtration followed by concentration <u>in vacuo</u> provided a yellow residue that was purified by flash chromatography to give the titled products (56 mg, 53%). The following spectral data were obtained from the two isomeric mixtures. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ:2.60 (s, 3H, $OCOCH_3$), 3.10 (m, 2H', HC<u>Ha,e</u>CHCO), 3.7 (m, 1H, CH-S), 3.74 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.81 (m, 2H, HC<u>Ha,e</u>-S), 7.73 (m, 2H, ArH), 8.06 (m, 2H, ArH), 8.59 (s, H, ArH). IR: (neat) 2960, 2922, 1770, 1738 (CO), 1662, 1634, 1623 (CO, quinone) cm^{-1}.

Example 8 : Preparation of tetrahydroanthraceno [2,3-c] thiopyran-3-yl derivatives



EXAMPLE 9

Step 1: t-Butyl acetoacetate 2-benzoate

To a stirred solution of t-butyl acetoacetate (10 ml, 60 mmol) in benzene (120 ml) and THF (60 ml) was added NaH (1.5g, 61 mmol) in portions after 15 minutes, benzoyl peroxide (2.91g, 12 mmol) dissolved in benzene (30 ml) was added. After 1 hour at room temperature, the reaction mixture was washed with 50 ml of saturated aqueous ammonium chloride, 2x50 ml of saturated aqueous sodium bicarbonate, and 50 ml of saturated aqueous sodium chloride. The organic layer was then dried over $MgSO_4$ and the solvent was removed in vacuo. The excess of t-butyl acetoacetate was removed by distillation under reduced pressure. The residue (2.4g, 72%) is obtained as a slightly yellow oil characterized as t-butyl acetoacetate 2-benzoate. ^1H NMR (300 MHz, $CDCl_3$) δ:1.52 (s, 9H,$-C(CH_3)_3$), 2.42 (s, 3H, $-CH_3$), 5.63 (s, 1H, -CH-O), 7.47 (dt, J=0.7 and 7.4 Hz, 2H, ArH), 7.61 (dt, J=0.7 and 7.4 Hz, 1H, ArH), 8.13 (dd, J=1.4 and 7.1 Hz, 2H, ArH).

Step 2: 3,6-dimethoxy-2-bromomethylene-1-(3-t-Butyl-carboxylate, 3-benzoate, 2-butanone 4-yl) benzene

To a stirred solution containing 500 mg, (1.55 mmol) of 3,6-dimethoxy, 1,2-dibromomethylene benzene and 684 mg (2.46 mmol) of t-Butyl acetoacetate-2-benzoate in 11 ml of acetonitrile and 6.5 ml of THF was added 1g of cesium carbonate. After 45 minutes, the reaction mixture was filtered over silica gel. The solvent was removed in vacuo, 948 mg of crude 3,6-dimethoxy,2-bromome-thylene 1-

(3-t-Butyl carboxylate, 3-benzoate, 2-butanone 4-yl) benzene was obtained. ^{1}H NMR (300 MHz, $CDCl_3$) δ:1.45 (s, 9H, $-C(CH_3)_3$), 2.41 (s, 3H, $-COCH_3$), 3.53 (s, 3H, $-OCH_3$), 3.82 (s, 3H, $-OCH_3$), 3.83 (2xd, J=14.8 Hz, 2H, ArH$\underline{CH_2}$-), 4.79 (s, 2H, $-CH_2$-Br), 6.72 (2xd, J=9.0 Hz, 2H, ArH), 7.38 (m, 2H, ArHCO-), 7.54 (m, 1H, ArHCO-), 7.81 (m, 2H, ArHCO-).

Step 3: **3,6-dimethoxy, 2-bromomethylene,1-(3-benzoate, 2-butanone,4-yl)-benzene**

To a stirred solution containing 948 mg of crude ß-Ketoester in 12 ml of acetone was slowly added 6 ml of HBr 48%. The reaction mixture was heated to 50°C for 105 minutes, then poured in 50 ml of water and 50 ml of ether, 100 ml of a saturated aqueous sodium bicarbonate was slowly added. The aqueous layer was extracted with 50 ml of ether. The organic layers were washed with 50 ml of a saturated aqueous sodium chloride, then dried over $MgSO_4$. Evaporation of the solvent gave 828 mg of a slightly yellow oil characterized as 3,6-dimethoxy 2-bromome-thylene, 1-(3-benzoate, 2-butanone, 4-yl) benzene. ^{1}H NMR (300 MHz, $CDCl_3$) δ:2.29 (s, 3H, $-COCH_3$), 3.24 (dd, J=9.0 and 14.3 Hz, 1H, -C$\underline{H_2}$-CH-O-), 3.45 (dd, J=4.6 and 14.3 Hz, 1H, -C$\underline{H_2}$-CH-O-), 3.81 (s, 3H, $-OCH_3$), 3.83 (s, 3H, $-OCH_3$), 4.80 (2xd, J=9.7Hz, 2H, $-CH_2$-Br), 5.51 (dd, J=4.6 and 9.0 Hz, 1H, -CH-O-), 6.77 (2xd, J=9.0 Hz, 2H, ArH), 7.43 (m, 2H, ArHCO-), 7.55 (m, 1H, ArHCO-), 7.95 (m, 2H, ArHCO-).

Step 4: **3,6-dimethoxy 2-(3-benzoate, 2-butanone, 4-yl) benzaldehyde**

To a stirred solution containing 828 mg of the crude benzylic bromide in 10 ml of dimethylsulfoxide was added 390 mg (4.65 mmol) of sodium bicarbonate. The reaction mixture was heated to 90°C for 25 minutes, then poured in 150 ml of water and extracted with 3x50 ml of ethyl ether. The organic layers were washed with 50 ml of a saturated aqueous sodium chloride, dried over $MgSO_4$ and the solvent was evaporated. The residue was flash chromatographed with hexanes-ethyl acetate 3-1 as the eluting solvent mixture. The titled compound was obtained in 60% yield (319 mg) for 3 steps. ^1H NMR (300 MHz, $CDCl_3$) δ:2.34 (s, 3H, $-COCH_3$), 3.65 (m, 2H, $ArH-CH_2-$), 3.81 (s, 3H, $-OCH_3$), 3.84 (s, 3H, $-OCH_3$), 5.42 (dd, J=5.1 and 9.1 Hz, 1H, -CH-O-), 6.85 (d, J=9.2Hz, 1H, ArH), 7.04 (d, J=9.2Hz, 1H, ArH), 7.41 (m, 2H, $ArHCO_2-$), 7.54 (m, 1H, $ArHCO_2-$), 8.00 (m, 2H, ArHCO-), 10.62 (s, 1H, -CHO).

Step 5: **3,6-dimethoxy 2-(3-hydroxy,2-butanone, 4-yl) benzaldehyde dimethyl acetal**

To a stirred solution containing 319 mg (0.93 mmol) of keto-aldehyde in 10 ml of methanol and 2 ml of methyl orthoformate was added 30 mg of p-toluenesulfonic acid. After 3.5 hours, 600 mg of potassium hydroxide and 3 ml of water were added and the reaction mixture was heated to reflux for 4 hours. The solution was then cooled and the methanol evaporated, 25 ml of water and 25 ml of ethyl ether were added. The aqueous layer was extracted with 2x25 ml of ethyl ether. The organic layers were washed with 25 ml of a saturated aqueous sodium chloride and dried over $MgSO_4$. Evaporation of the solvent gave 280 mg as an

oil of crude 3.6-dimethoxy 2-(3-hydroxy, 2-butanone, 4-yl) benzaldehyde dimethyl acetal. ^{1}H NMR (300 MHz, $CDCl_3$) δ:1.33 (s, 1H, $-CH_3$), 3.03 (dd, J=2.9 and 13.9 Hz, 1H, $-C\underline{H}_2-CH-O-$), 3.26 (s, 3H, $-OCH_3$), 3.27 (m, 1H,$-C\underline{H}_2-CH-O$), 3.30 (s, 3H, $-OCH_3$), 3.31 (s, 3H, $-OCH_3$), 3.53 (s, 3H, $-OCH_3$), 3.75 (s, 3H, $-OCH_3$), 3.76 (s, 3H, $-OCH_3$), 4.07 (m, 1H, -CH-O-), 4.17 (d, J=6.6 Hz, 1H,-OH), 5.86 (s, 1H, ArHC$\underline{H}$-O), 6.75 (2xd, J=9.0 Hz, ArH).

Step 6: **Methyl 1,5,8-trimethoxyisochroman-3-yl-ketone dimethyl acetal**

To a stirred solution containing 280 mg of the crude product from step 5 in 4 ml of methanol was added 30 mg of pyridinium p-toluenesulfonate. After 30 minutes, 100 µl of triethylamine was added and methanol was evaporated. The residue was dissolved in methylene chloride and filtered over silica gel. The solvent was evaporated and the residue was purified (not necessary, the crude is clean by NMR) by flash chromatography with henanes-ethyl acetate 2:1 as the eluting solvent mixture. The isochroman analog was obtained in greater then 80% yield (225 mg) for 2 steps. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.40 (s, 3H, $-CH_3$), 2.47 (dd, J=11.8 and 17.6 Hz, 1H, -C$\underline{H}$a-CH-), 2.79 (dd, J=3.8 and 17.6 Hz, 1H, -C$\underline{H}$e-CH-), 3.29 (s, 3H, $-OCH_3$), 3.32 (s, 3H, $-OCH_3$), 3.62 (s, 3H,$-OCH_3$), 3.78 (s, 3H, $-OCH_3$), 3.81 (s, 3H, $-OCH_3$), 4.35 (dd, J=3.8 and 11.8 Hz, 1H, $-CH_2-C\underline{H}-O$), 5.63 (s, 1H, ArH-C$\underline{H}$-O), 6.73 (2xd, J=8.9 Hz, 2H, ArH).

Step 7: **Methyl(methoxy-1,5,8-dioxo-5,8-dihydroisochroman-3-yl) ketone**

To a stirred solution of I (7 mg, 0.023 mmol) in acetonitrile (0.5 ml) at 0°C was slowly added Ceric ammonium nitrate (CAN) (44 mg, 0.069 mmol) in water (0.5 ml). After 30 minutes, water (10 ml) was added and the mixture was extracted with CH_2Cl_2. The organic phases were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo to give a yellow oil (II) which did not need any purification. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.34 (s, 3H, -CO-CH_3), 2.39 (dd, J=11.3 and 19.8 Hz, 1H, -C<u>H</u>a-CH), 2.85 (dd, J=4.1 and 19.8 Hz, 1H, -C<u>H</u>e-CH), 3.61 (s, 3H, -OMe), 4.48 (dd, J=4.1 and 11.3 Hz, 1H, CH_2-C<u>H</u>-O), 5.52 (s, 1H, ArH-C<u>H</u>-O), 6.78 (2xd, J=10.2 Hz, 2H, ArH).

Step 8 **Methyl(1-methoxy-6 and 11-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno (2,3-c) pyran-3-yl)ketone**

To a stirred mixture of NaH (8.7 mg, 0.36 mmol) in THF (2 ml) at 0°C was added homophtalic anhydride (57 mg, 0.35 mmol). After 10 minutes, I (79 mg, 0.35 mmol) in THF (2 ml) was added and the reaction mixture was warmed up to room temperature. After 1 hour HCl 1N (10 ml) was added and the mixture was extracted with CH_2Cl_2. The organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was purified by flash chromatography using toluene-acetone 95:5 gave 13 mg (10% yield) of II. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.36 (s, 3H, -CO-CH_3), 2.55 (dd, J=11.8 and 19.7 Hz, 1H, -C<u>H</u>a-CH-O), 3.07 (dd, J=4.1 and 19.7 Hz, 1H, -C<u>H</u>e-CH-O), 3.68 (s, 3H, -OCH_3), 4.56 (dd, J=4.1 and 11.8 Hz, 1H, -CH-CO), 5.71 (s,

1H, -O-CH-O), 7.7 (m, 2H, ArH), 7.95 (dd, J=1.6 and 7.1 Hz, 1H, ArH), 8.09 (s, 1H, ArH), 8.46 (dd, J=1.6 and 8.7 Hz, 1H, ArH).

Step 9: **Methyl 5,8-dimethoxy-1-hydroxyisochroman-3-yl ketone**

To a stirred solution of crude product from step 5 (1.89g; 5.49 mmol) in a mixture of acetone (80 ml) and water (25 ml) was added p-toluene sulfonic acid monohydrate (70 mg; .37 mmol). After stirring at room temperature for 3 hours, triethylamine (2 ml; 1.43 mmol) was added and stirred for 5 minutes. The mixture was evaporated until volume went down to 10 ml. A mixture of acetone (80 ml) and water (15 ml) was added followed by addition of p-toluene sulfonic acid monohydrate (70 mg; .37 mmol). After 3.5 hours, triethylamine (3 ml; 2.15 mmol) was added, evaporated to a small volume, extracted with ether (3x100 ml). The extract was washed with brine (50 ml), dried over $MgSO_4$ and evaporated yielding quite pure 1-hydroxyisochroman (1.3g; 94%), (MP. 136-138°C). NMR ($CDCl_3$; 300 MHz) δ: 2.32 (3H, s, CH_3O), 2.51 (1H, dd, J=12.4, 17.5 Hz, H-4), 2.97 (1H, d, J=3.5 Hz; -OH), 3.06 (1H, dd, J=4.1, 17.5 Hz, H-4), 3.77, 3.82 (3H, s each, $ArOCH_3$), 4.70 (1H, dd, J=4.1, 12.4 Hz, H-3), 6.22 (1H, d, J=3.4 Hz, 1H), 6.71, 6.76, (1H, d each, J=9.0 Hz, ArH).

Step 10: Methyl(hydroxy-1,5,8-dioxo-5,8-dihydroisochroman-3-yl) ketone

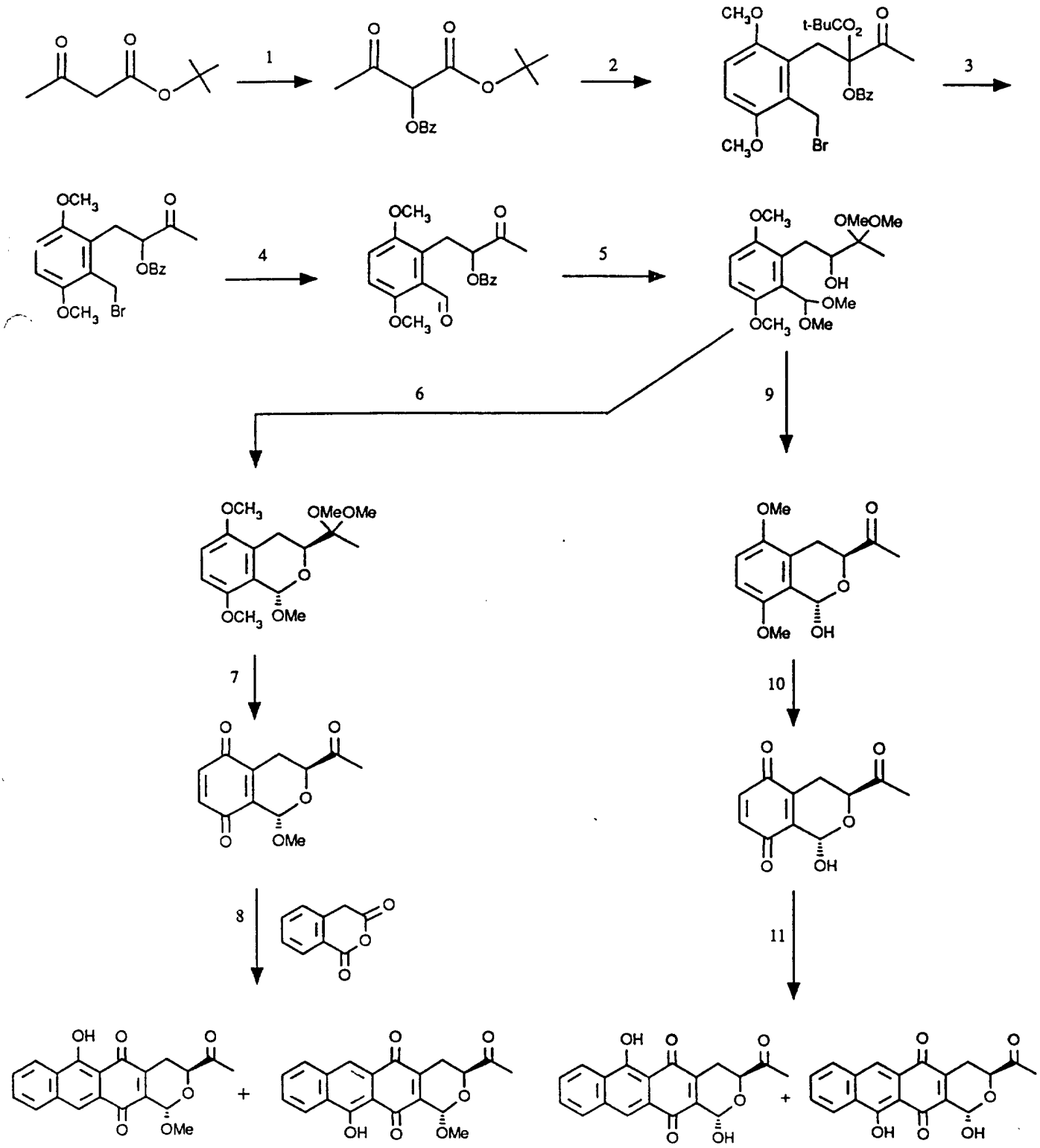
To a stirred solution of I (123 mg, 0.488 mmol) in acetonitrile (10 ml) at 0°C was slowly added Ceric ammonium nitrate (CAN) (802 mg, 1.46 mmol) in water (6 ml). After 30 minutes, water (40 ml) was added and the mixture was extracted with CH_2Cl_2. The organic phases were washed with brine and dried over $MgSO_4$, filtered and concentrated in vacuo to give a yellow oil (II) which did not need any purification (106 mg, 98%). ^1H NMR (300 MHz, $CDCl_3$) δ: 2.31 (s, 3H, $-CO-CH_3$), 2.39 (dd, J=11.5 and 19.6 Hz, 1H, -CHa-CH), 2.88 (dd, J=4.2 and 19.6 Hz, 1H, -CHe-CH), 3.90 (broad s, 1H, -OH), 4.65 (dd, J=4.2 and 11.5 Hz, 1H, CH_2-CH-O), 6.04 (s, 1H, ArH-CH-O), 6.80 (2d, J=10.2 Hz, 2H, ArH).

Step 11: Methyl(1-hydroxy-6 and 11-hydroxy-5,12-dioxo-3,4-5,12- tetrahydroanthraceno(2,3-c)pyran-3-yl)ketone

To a stirred solution of homophtalic anhydride (87 mg, 0.536 mmol) in THF (6 ml) at 0°C was added a solution of sodium bis (trimethylsilyl) amide (0.536 mmol, 536 µl) 1M in THF. After 5 minutes the reaction mixture was cooled down to -78°C and a solution of I (obtained from hydroxyquinone (119 mg, 0.536 mmol), methoxypropene (300µl) and catalytic amount of pyridinium p-toluenesulfonate) in CH_2Cl_2 (2 ml). After 1 hour at -78°C the reaction mixture was warmed up to room temperature for 2.5 hours then HCl 1N (5 ml) was added and after 5 minutes the mixture was extracted with CH_2Cl_2. The organic phases were washed with brine, dried over $MgSO_4$, filtered and concentrated in

vacuo. The residue was purified by flash chromatography using toluene-acetone 90:10 gave 12 mg (7% yield) of II. ^{1}H NMR (300 MHz, DMSO) δ: 2.26 (s, 3H, -CO-CH_3), 2.49 (dd, J=11.5 and 19.4 Hz, 1H, -CHa-CH-O), 2.85 (dd, J=4.2 and 19.4 Hz, 1H, -CHe-CH-O), 4.64 (dd, J=4.2 and 11.5 Hz, 1H, -CH-CO), 5.95 (d, J=6.2 Hz, 1H, -O-CH-O), 6.26 (d, J=6.2 Hz, 1H, -OH), 7.81 (m, 2H, ArH), 8.13 (s, 1H, ArH), 8.22 (d, J=7.7 Hz, 1H, ArH), 8.36 (d, J=8.0 Hz, 1H, ArH), 13.71 (s, 1H, ArOH).

Example 9 : Short synthesis of anthraceno [2,3-c] pyran-3-yl aglycones with a methyl ketone side chain



EXAMPLE 10

Step 1: N,N-diethyl(2,5-dimethoxy)benzamide

To a stirred solution of 2,5-dimethoxybenzoic acid (6.61g, 36.3 mmol) in 50 ml of CH_2Cl_2 was added a solution of $(COCl)_2$ in CH_2Cl_2 (2.0M, 20 ml, 40.0 mmol) at 0°C under argon. After addition of catalytic amount of pyridine (0.2 ml) an evolution of gas was observed. The reaction was warmed up to room temperature and stirred for 3 hours. The volatile were removed and the residue was dissolved in 300 ml of diethyl ether. Diethylamine (5.26 ml, 50.8 mmol) was introduced dropwise at 0°C under argon. The resulting mixture was stirred at room temperature for another 3 hours, and then quenched with saturated K_2CO_3 solution. The organic layer was washed with 2N NaOH and water, dried over $MgSO_4$, filtered and then evaporated. Flash chromatography of the residue with CH_2Cl_2 and CH_3CO_2Et (1:1) provided pure title compound (8.34g, 35.1 mmol) in 97% yield as white solid. ^1H NMR ($CDCl_3$) δ: 1.05 (3H, t, J=7.1 Hz), 1.24 (3H, t, J=7.1 Hz), 3.16 (2H, q, J=7.1 Hz), 3.56 (2H, m), 3.77 (3H, s), 3.78 (3H, s), 6.77 (1H, m), 6.84 (2H, m).

Step 2: N,N-diethyl(2,5-dimethoxy-6-methyl)benzamide

To a stirred solution of TMEDA (2.23 ml, 14.8 mmol) in 25 ml of THF was added s-BuLi (1.3M, 11.35 ml, 14.8 mmol) at -78°C under argon. After 20 minutes, a solution of N,N-diethyl(2,5-dimethoxy)benzamide (1.4g, 5.9 mmol) in 5 ml of THF was introduced dropwise at -78°C. The stirring was continued at
-78°C for 1 hour before MeI (1.40 ml, 22.5 mmol) was added. The resulting mixture was stirred at -78°C for 1 hour, followed by addition of 20 ml saturated NH_4Cl solution.

The reaction mixture was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$, filtered and concentrated. Flash chromatography of the residue with CH_2Cl_2 and ethyl acetate (1:1) gave pure title compound (1.42g, 5.66 mmol) in 96% yield. ^1H NMR ($CDCl_3$) δ: 1.02 (3H, t, J=7.2 Hz), 1.26 (3H, t, J=7.2 Hz), 2.11 (3H, s), 3.12 (2H, q, J=7.2 Hz), 3.45 (2H, m), 3.75 (3H, s), 3.79 (3H, s), 6.68 (1H, d, J=8.9 Hz), 6.76 (1H, d, J=8.9 Hz).

Step 3: **3,4-dihydro-5,8-dimethoxy-3-vinylisocoumarin**

To a stirred solution of the benzamide from step 2 above (3.51g, 14.0 mmol) in 140 ml of THF at -78°C under argon was added n-butyllithium (2.5M, 9.0 ml, 22.5 mmol) dropwise, generating a red solution. After stirred for 30 minutes, acrolein (2.25 ml, 33.6 mmol) was added. The stirring was continued at -78°C for 1 hour before it was quenched with 100 ml of saturated NH_4Cl solution. The mixture was extracted with CH_2Cl_2, and the combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered and concentrated to a residue. Without further purification, the residue was dissolved in 180 ml of benzene and then heated to reflux in the presence of camphorsulfonic acid (2.93g, 12.6 mmol) for 5 days. After cooled to room temperature, 200 ml of $NaHCO_3$ (5%) and 200 ml of CH_2Cl_2 were added. The organic layer was washed with H_2O, dried over $MgSO_4$, filtered and then concentrated. Flash chromatography of the residue with CH_2Cl_2, hexane, and ethyl acetate (2:4:1) provided the title isocoumarin (1.28g, 5.47 mmol) in 39% overall yield. ^1H NMR ($CDCl_3$) δ:2.76 (1H, dd, J=16.9, 10.9 Hz), 3.22 (1H, dd, J=16.9, 3.3 Hz), 3.83 (3H, s), 3.91 (3H, s), 4.85 (1H, m), 5.29 (1H, dd, J=10.6, 1.1 Hz), 5.44 (1H, dd, J=17.3, 1.1 Hz), 6.0 (1H, m), 6.88 (1H, d, J=9.1 Hz), 7.06 (1H, d, J=9.1 Hz).

Step 4: 3,4-dihydro-1,5,8-trimethoxy-3-vinylisocoumarin

To a stirred solution of the isocaumarin from step 3 above (9.4 mg, 0.4 mmol) in 8 ml of toluene was added dropwise a solution of DIBAL-H (1M, 0.50 ml, 0.50 mmol) at -78°C under argon. The resulting mixture was stirred at -78°C for 1.5 hour before Na_2SO_4 10 H_2O (100 mg, 0.31 mmol). After the reaction was warmed to room terperature, it was filtered to remove the solids, and washed with acetone. The filtrate was evaporated to give an oily residue which contained the corresponding lactol. Without further purification, the residue was treated with 5 ml of CH_3OH, 1 ml of $CH(OMe)_3$, and PTSA (30 mg, 0.16 mmol) at room temperature for 10 minutes. The solvents were removed by rotavapor and the residue was purified by flash chromatography with hexane and ethyl acetate (7:3) to give pure title isocoumarin (65 mg, 0.26 mmol) in 65% overall yield. ^1H NMR ($CDCl_3$) δ: 2.47 (1H, dd, J=17.2, 12.0 Hz), 2.85 (1H, dd, J=17.2, 3.6 Hz), 3.56 (3H, s), 3.78 (3H, s), 3.82 (3H, s), 4.63 (1H, m), 5.24 (1H, dt, J=10.6, 1.4 Hz), 5.43 (1H, dt, J=17.3, 1.4 Hz), 5.63 (1H, s), 6.05 (1H, m), 6.70 (1H, d, J=8.9 Hz), 6.76 (1H, d, J=8.9 Hz).

Step 5: 1-methoxy-3-vinylisochroman-5,8-dione

To a stirred solution of the isocoumarin from step 4 above (30 mg, 0.12 mmol) in 2 ml of CH_3CN was added dropwise a solution of $(NH_4)_2Ce(NO_3)_6$ in 1 ml of H_2O at 0°C. After 5 minutes, the reaction was warmed to room temperature and stirred for another 30 minutes. The reaction mixture was diluted with 10 ml of CH_2Cl_2 and 10 ml

of H_2O. The organic layer was washed with H_2O, dried over $MgSO_4$, filtered and then concentrated to a residue that was purified by flash chromatography (hexane/ethyl acetate; 7:3) to provide pure product (15 mg, 0.07 mmol) in 57% yield along with a by-product (10 mg, 0.05 mmol, 40%). The by-product could be converted to desired product in 92% yield by treating it with $CH(OMe)_3$ in MeOH with PTSA at room temperature. ^1H NMR ($CDCL_3$) δ: 2.29 (1H, dd, J=19.4, 11.4 Hz), 2.65 (1H, dd, J=19.4, 3.6 Hz), 3.55 (3H, s), 4.52 (1H, m), 5.27 (1H, dd, J=10.5, 1.4 Hz), 5.41 (1H, dd, J=17.3, 1.4 Hz), 5.43 (1H, s), 5.98 (1H, m), 6.74 (1H, d, J=10.2 Hz), 6.78 (1H, d, J=10.2 Hz).

Step 6: **6-hydroxy-1-methoxy-1,2,3,4-tetrahydro-3-vinyl-(2-oxygen) naphthacene-5,12-dione**

To a stirred solution of i-Pr_2NH (0.254 ml, 1.8 mmol) in 6 ml of THF was added a solution of n-BuLi (2.5M, 0.725 ml, 1.8 mmol) at 0°C under argon. After stirring for 20 minutes, the newly made LDA solution was cooled to -78°C and stirred for additional 5 minutes. A solution of homophthalic anhydride (294 mg, 1.8 ml) in 4 ml of THF was added dropwise, causing the color change from yellow, green and then to yellowish. Upon stirring for 5 minutes after completion of the addition, a solution of the quinone from step 5 above (332 mg, 1.5 mmol) in 4 ml of THF was quickly injected. The resulting mixture was stirred at -78°C for 20 minutes at room temperature for 2 hours and then placed in the fridge overnight. The mixture was quenched with 10 ml saturated NH_4Cl solution and partitioned between 1N HCl and CH_2Cl_2. The organic layer was washed with H_2O, dried over $MgSO_4$, filtered and then concentrated to a residue

that was purified by flash chromatography with hexane, CH_2Cl_2, ethyl acetate (2:2:1) to give title compound (276 mg, 0.82 mmol) in 55% yield as a single regioisomer. MP: 150°C (decomposes). ^1H NMR ($CDCl_3$) δ:2.46 (1H, dd, J=19.2, 11.4 Hz), 2.89 (1H, dd, J=19.4, 3.7 Hz), 3.61 (3H, s), 4.60 (1H, m), 5.30 (1H, dd, J=10.6, 1.3 Hz), 5.45 (1H, dd, J=17.3, 1.4 Hz), 5.63 (1H, s), 6.04 (1H, m), 7.70 (2H, m), 7.95 (1H, d, J=7.4 Hz), 8.11 (1H, s), 8.48 (1H, d, J=7.3 Hz), 13.83 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 27.80, 56.85, 66.90, 94.11, 117.31, 122.41, 125.43. 128.64, 129.68, 130.42, 131.11, 131.87, 136.63, 137.49, 142.12, 144.99, 163.21, 181.95, 188.66.

Step 7: **6-acetoxy-1-methoxy-1,2,3,4-tetrahydro-3-vinyl-(2-oxygen)naphthacene-5,12-dione**

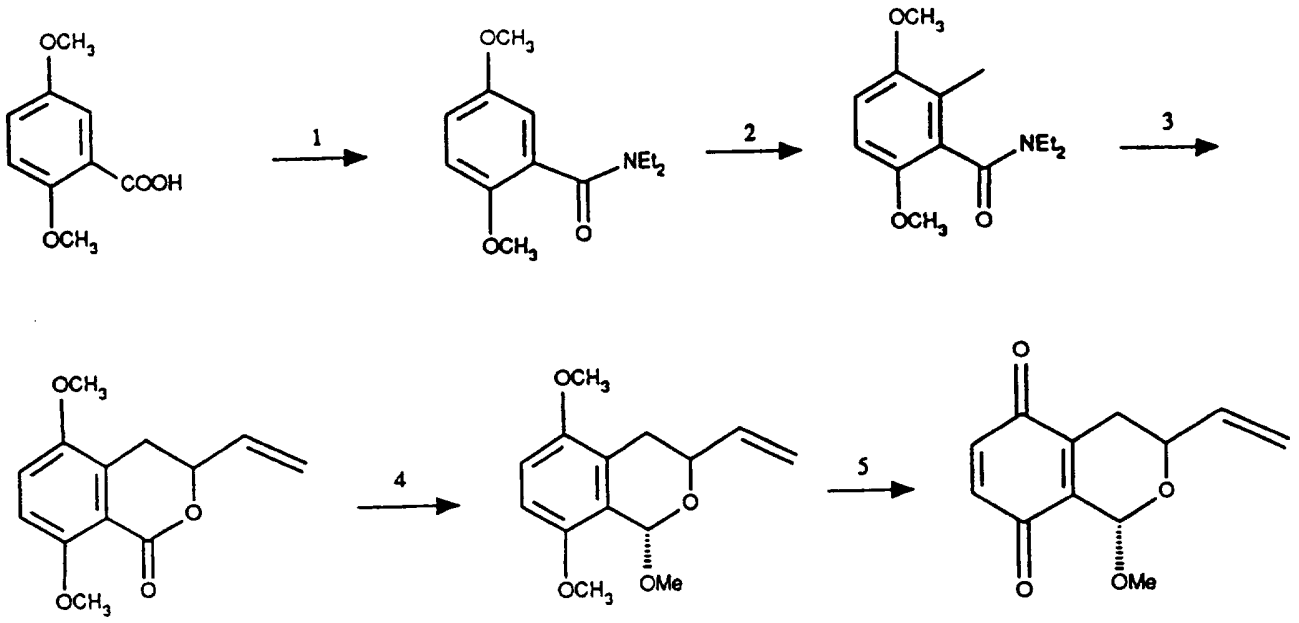
To a stirred solution of the tetracyclic quinone from step 6 above (230 mg, 0.68 mmol) in 35 ml of CH_2Cl_2 were added 7 ml of pyridine, 7 ml of Ac_2O, and 123 mg of DMAP (1.00 mmol) at room temperature. The mixture was then stirred for 2 hours before it was poured into a mixture of ice water (20 ml) and CH_2Cl_2 (20 ml). The organic layer was washed with H_2O, 0.1N HCl, dried over $MgSO_4$, filtered and then concentrated to a crude residue that was purified by flash chromatography to give the title compound (178 mg, 0.47 mmol) in 69% yield as yellow solid. MP 228-229°C, IR (neat) 1208, 1611, 1643, 1667, 1763, 2912 CM^{-1}, ^1H NMR ($CDCl_3$) δ: 2.41 (1H, dd, J=19.0, 11.0 Hz), 2.61 (s, 3H), 2.82 (1H, dd, J=19.0, 3.5 Hz), 3.61 (3H, s), 4.58 (1H, m), 5.29 (1H, dd, J=11.0, 1.5 Hz), 5.44 (1H, dd, J=17.0, 1.5 Hz), 5.64 (1H, s), 6.01 (1H, m), 7.72 (2H, m), 8.06 (1H,

m), 8.14 (1H, m), 8.59 (1H, s), ^{13}C NMR ($CDCl_3$) δ:21.14, 27.78, 56.22, 93.43, 116.62, 123.77, 127.00, 128.61, 130.01, 130.16, 130.24, 130.31, 135.52, 136.93, 139.80, 145.38, 168.90, 181.70, 182.50.

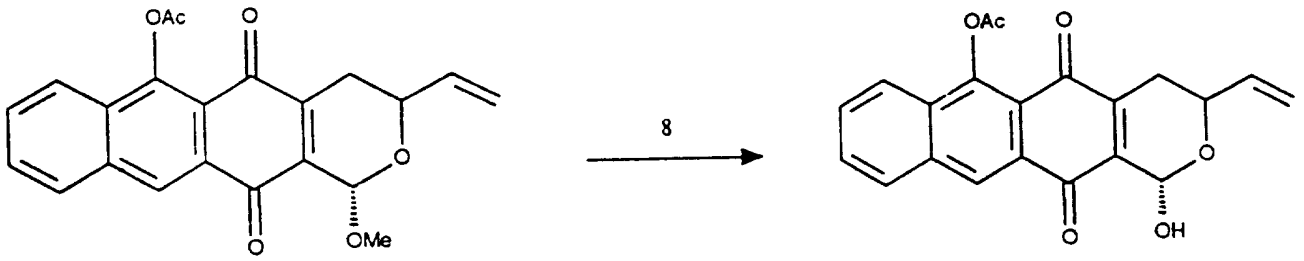
Step 8: **6-acetoxy-1-hydroxy-1,2,3,4-tetrahydro-3-vinyl-(2-oxygen)naphthacene-5,12-dione**

To a stirred solution of the tetracycle form step 7 above (16 mg, 42 mmol) in 3 ml of CH_2Cl_2 was added a solution of B-bromo-9-BBN in CH_2Cl_2 (1M, 0.105 ml, 105 mmol) at 0°C under argon. After stirred at 0°C for 1h, 3 ml of ice water was added. The reaction mixture was extracted with CH_2Cl_2, washed with water, dried over $MgSO_4$, filtered, and then concentrated to a crude residue that was purified by flash chromatography (hexane, CH_2Cl_2, ethyl acetate, 2:2:1) to give title compound (4 mg, 11 mmol) in 26% yield. IR (neat) 1191, 1610, 1640, 1770, 2919, 3440 $CM^{-1}{}_3$, ^1H NMR ($CDCl_3$) δ: 2.43 (1H, dd, J=19.0, 11.0 Hz), 2.60 (3H, s), 2.86 (1H, dd, J=19.0, 3.5 Hz), 4.61 (1H, M), 5.28 (1H, dd, J=11.0, 1.5 Hz), 5.42 (1H, dd, J=17.0, 1.5 Hz), 5.62 (1H, br, s), 5.81 (1H, s), 6.00 (1H, m), 7.73 (2H, m), 8.67 (1H, m), 8.14 (1H, m), 8.63 (1H, s).

Example 10: Preparation of tetrahydroanthraceno [2,3-c] pyran-3-yl derivetive with a vinyl side chain



BCH 712



BCH 716

EXAMPLE 11

Step 1: **Methyl 2-methoxyisopropyloxy-acetate**

To a stirred solution of methyl glycolate (5 ml, 64.8 mmol) and 2-methoxypropene (12.5 ml, 130.5 mmol) in dry dichloromethane (15 ml) at 0°C was added catalytic amount of pyridinium p-toluene-sulfonate (100 mg). The mixture was stirred at 0°C for 2 hours. Saturated sodium bicarbonate solution was added and methylene chloride layer was separated, dried over anhydrous magnesium sulfate. Solvent was evaporated and the product was distilled over anhydrous potassium carbonate under reduced pressure (20 mmHg) at 62°-64°C (yield = 9.9g, 94%), ^{1}H NMR (300 MHz, D_6-acetone) δ:1.28 (6H, s), 3.15 (3H, s), 3.67 (3H, s), 4.01 (2H, s).

Step 2: **Methyl 3-(2'bromomethyl-3'-6'-dimethoxy)phenyl-2-methoxyisopropyloxy propionate**

To a solution of cyclohexylisopropylamine (1.6 ml, 9.8 mmol) in dry THF (30 ml) at 0°C was added 2.5M BuLi in hexanes (3.95 ml, 9.8 mmol). After stirring at 0°C for 10 minutes, the mixture was cooled to -78°C. The protected methyl glycolate from step 1 (1.59g, 9.7 mmol) in THF (6 ml) was added. After stirring for 15 minutes at -78°C, 1,2-dibromomethyl-3,6-dimethoxybenzene (1.5g, 5.1 mmol) in dry THF (16 ml) was added followed by addition of HMPA (2 ml) in 10 minutes. The mixture was stirred at -78°C for 1 hour. Temperature was then raised to -40°C slowly during the next 50 minutes. Saturated NH_4Cl solution (20 ml) was added, THF was removed at 25°C and the residue was extracted with ether. Ether extract was washed with sat.

$NaHCO_3$, dried over $MgSO_4$, evaporated and the residue was chromatographed over silica gel washed with 5% triethylamine (eluent: hexanes/EtOAc = 4:1), yielding 1.37g (66%) of the title compound. ^1H NMR (300 MHz, d_6-acetone) δ:1.05 (3H, s, CH_3), 1.15 (3H, s, CH_3), 2.78 (3H, s, OMe), 3.01 (1H, dd, J=8.9, 13.5 Hz, H-3), 3.66 (3H, s, CO_2Me), 3.83 (6H, s, $ArOCH_3$), 4.43 (1H, dd, J=5.0, 8.8 Hz, H-2), 4.81 (2H, s, $ArC\underline{H}_2Br$), 3.21 (1H, dd, J=5.1, 13.5 Hz, H-3), 6.88, 6.95 (1H, d, each, J=9 Hz, ArH).

Step 3: **Methyl 3-(2'-bromomethyl-3'-6'-dimethoxy)phenyl-2-hydroxy propionate**

To a solution of methyl 3-(2'-bromomethyl-3'-6'-dimethoxy)-phenyl-2-methoxy-isopropyloxy propionate (29g, 71 mmol) in diethyl ether (40 ml) was added 1N HCl (20 ml). After stirring at ambient temperature for three hours, ether layer was separated, washed with brine, dried over $MgSO_4$ and evaporated to give the title product as an oil in quantitative yield. ^1H NMR (300 MHz, $CDCl_3$) δ:3.10 (1H, dd, J=8.7, 13.9 Hz, H-3), 3.29 (1H, dd, J=13.8, 4.3 Hz, H-3) 3.77 (3H, s, CO_2Me), 3.79, 3.83 (3H, s, each, ArOMe), 4.47 (1H, dd, J=8.7, 4.5 Hz, H-2), 4.72 (2H, s, $ArC\underline{H}_2$), 6.74, 6.80 (1H, d, each, J=9.0 Hz, ArH).

Step 4: **5,8-dimethoxy-isochroman-3-yl-formic acid**

To a solution of methyl-3(2'-bromomethyl-3'-6'-dimethoxy) phenyl-2-hydroxy propionate (30 mg, .09 mmol) in dry THF (3 ml) was added sodium hydride (60% dispersion in oil, 25 mg, .6 mmol). The mixture was stirred at 50°C for 2.5 hours. Small amount of ice was carefully added, extracted with dichloromethane. Aqueous portion was acidified with dil. HCl, extracted with EtOAc, washed with brine, dried and evaporated (yield ~85%). ^1H NMR (300 MHz,

$CDCl_3$) δ: 2.74 (1H, dd, J=11.2, 17.1, H-2, H-4), 3.19 (1H, ddd, J=1.3, 3.8, 17.1 Hz, H-4), 3.74, 3.77 (3H, s, each, OMe), 4.26 (1H, dd, J=3.9, 11.2, H-3) 4.7 (1H, d, J=15.9, H-1), 5.06 (1H, d, J=15.9, H-1), 6.63 and 6.67 (1H, d, each, J=12.2, aromatic protons).

Step 5: Methyl 3-(2'-formyl-3',6'-dimethoxy)phenyl-2-methoxyisopropyloxypropionate

Methyl 3-(2'-bromomethyl-3',6'-dimethoxy)phenyl-2-methoxyisopropyloxy propionate (1.2g, 2.9 mmol) was dissolved in dry DMSO (25 ml) and sodium bicarbonate (622 mg, 7.4 mmol) was added. The mixture was stirred at 95°C for 45 minutes. It was cooled, quenched with water (125 ml), extracted with ether (3x200 ml). Extracts were washed with brine (25 ml) dried over $MgSO_4$. Solvent was evaporated, yielding 9g of the title compound (90%). ^1H NMR data (300MHz, d_6-acetone) δ:1.16 (3H, s, CH_3), 1.18 (3H, s, CH_3), 2.99 (3H, s, OCH_3), 3.53 (3H, s, CO_2Me), 3.82 (3H, s, ArOH), 3.88 (3H, s, ArOMe), 7.04 (1H, d, J=10.0 Hz, ArH), 7.21 (1H, d, J=10.0 Hz, ArH), 10.50 (1H, s, CHO).

Step 6: Methyl-5,8-dimethoxy-1-hydroxyisochroman-3-yl-formate

To a solution of methyl-3-(2'-formyl-3'-6'-dimethoxy)phenyl-2-methoxyisopropyloxy-propionate (4.2g, 12.4 mmol) in THF (75 ml) containing water (4 ml) was added pyridinium p-toluenesulfonate (230 mg). After stirring at room temperature for 1.75 hours, triethylamine (3 ml) and

saturated NH_4Cl solution (60 ml) were added. THF was removed at 25°C and the mixture was extracted with ether (3x150 ml). Ether extract was washed with brine, dried and evaporated yielding 3.9g of 1-hydroxyisochroman (95%) (quite pure from NMR spectrum). (MP. 127-129°C) ^1H NMR (300 MHz, $CDCl_3$) δ: 2.69 (1H, dd, J=12.3, 17.6 Hz, H-4), 3.07 (1H, broad peak, OH), 3.13 (1H, dd, J=17.5, 3.8 Hz, H-4), 3.78 (3H, s, CO_2Me), 3.82, 3.83 (3H, s, each, ArOMe), 4.91 (1H, dd, J=12.3, 3.8 Hz, H-3), 6.24 (1H, br, s, H-1), 6.71 and 6.77 (1H, d, each, J=8.9 Hz, ArH).

Step 7: 1-Hydroxy-3-carbmethoxy-5,8-dioxoisochroman

To a stirred solution of the isochroman from step 6 above (232 mg, 0.865 mmol) in 10 ml of CH_3CN was added a solution of cerium ammonium nitrate (1.422g, 2.59 mmol) in 7 ml of H_2O at 0°C. The reaction mixture was slowly warmed to room temperature and stirred for 15 minutes. After it was quenched with H_2O (20 ml), the mixture was extracted with CH_2Cl_2 (2 x 50 ml). The combined organic layers were dried over $MgSO_4$, filtered, concentrated to a residue that was found to be pure title compound and used for next reaction without further purification (201 mg, 0.844 mmol, 98%). ^1H NMR ($CDCl_3$) δ: 2.55 (1H, m), 2.95 (1H, dd, J=19.5, 4.0 Hz), 3.15 (1H, br s), 3.84 (3H, s), 4.86 (1H, m), 6.04 (1H, s), 6.79 (2H, m).

Step 8: 3-Carbmethoxy-1,11-dihydroxy-1,2,3,4-tetrahydro-(2-oxygen) naphthacene-5,12-dione
3-Carbmethoxy-1,6-dihydroxy-1,2,3,4-tetrahydro-(2- oxygen)naphthacene-5,12-dione

To a freshly made LDA solution (1.7 mmol, 5 ml of THF) at -78°C was added dropwise a solution of homophathalic anhydride I (189.7 mg, 1.17 mmol) in 4 ml of THF under argon over 15 minutes. After stirring at -78°C for 5 minutes, a solution of quinone II (1.15 mmol) in 4 ml of THF was injected. Stirring was continued at -78°C for 1 hour and then at room temperature for 2 hours. After kept in fridge for overnight, the whole mixture was poured into 25 ml of 1N HCl solution. The reaction mixture was extracted with CH_2Cl_2 (20 ml x 3). The combined orgaic phases were washed with water, dried over $MgSO_4$, filtered and then concentrated to a crude residue that was purified by flash chromatographied to give a mixutre of III and IV (1:1, 130.0 mg, 32%). The following spectral data were obtained from the two regioisomeric mixtures. I.R. (neat) 146g, 1501, 1612, 1658, 1742, 2952, 3428 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.71 (2H, m), 3.18 (2H, m), 3.18 (2H, m), 3.87 (3H, s), 3.88 (3H, s), 4.92 (2H, m), 6.23 (1H, s), 6.27 (1H, s), 7.71 (4H, m), 7.95 (2H, d, J=7.7 Hz), 8.10 (1H, s), 8.12 (1H, s), 8.46 (2H, d, J=7.6 Hz), 13.75 (1H, s), 13.77 (1H, s).

Step 9: Methyl (1,5,8-trimethoxyisochroman-3-yl)formate

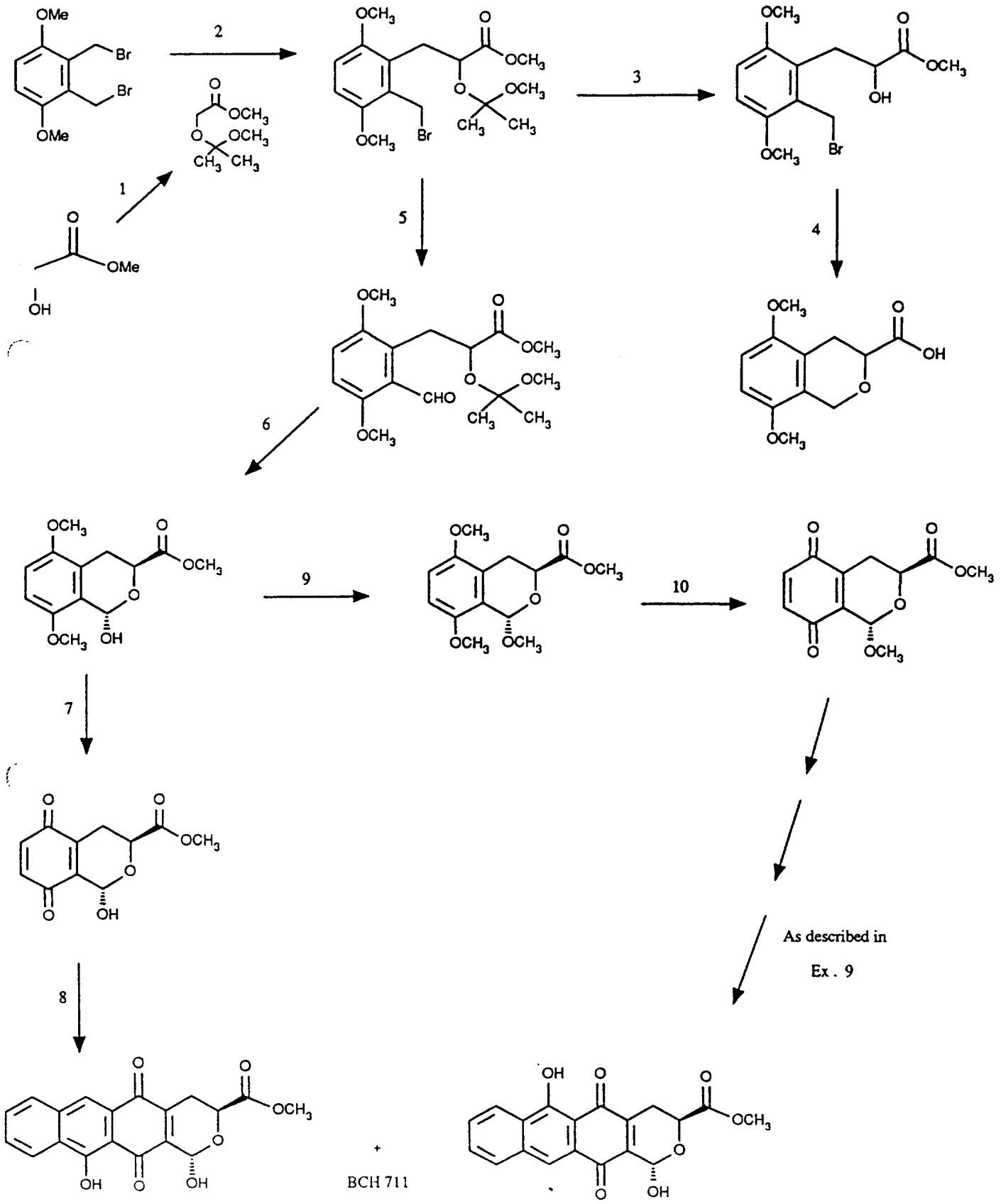
The compound from step 6 above was treated at room temperature with excess trimethyl orthoformate in methanol for twelve hours. A quantitative yield of the titled compound was obtained. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.71 (dd, 1H, J=12.4, 17.3 Hz, HC<u>Ha</u>), 3.10 (dd, 1H, J=4.0, 17.3 Hz, HC<u>He</u>), 3.59 (s, 3H, CO_2CH_3), 3.79 (s, 3H, OCH_3), 3.81

(s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.80 (dd, 1H, J=4.0, 12.4 Hz, O-CH), 5.71 (s, 1H, O-CH-O), 6.74 (2d, 2H, HC=H).

Step 10: Methyl (1-methoxy-5,8-dioxo-5,8-dihydioisochroman-3-yl)formate

This compound was obtained in 90% yield by using the procedure in step 7, example 9. ^1H NMR (300 MHz, $CDCl_3$) δ: 2.54 (ddd, 1H, J=1.2, 11.7, 19.5 Hz, HCHa), 2.88 (dd, 1H, J=4.1, 19.5 Hz, HCHe), 3.53 (s, 3H, CO_2CH_3), 3.57 (s, 3H, OCH_3), 4.10 (dd, 1H, J=4.1, 11.7 Hz, OCH0), 5.49 (s, 1H, O-CH-O), 6.75 (2d, 2H, HC=CH).

Example 11: Short synthesis of anthraceno [2,3-c] pyran-3-yl derivatives with an ester side chain



EXAMPLE 12

Step 1: 2,5-dimethoxy-6-hydroxymethyl benzaldehyde dioxane acetal

To a solution of 2,5-dimethoxybenzaldehyde dioxane acetal (10.5g, 46.9 mmol) in dry ether (200 ml) at -10°C was added 2.5M BuLi (30 ml, 75 mmol). The mixture was stirred at -7°C for 5.5 hours. Dry paraformaldehyde (2.6g) was quickly added and the mixture was stirred at 0°C for 2 hours. It was stirred at room temperature overnight, poured into saturated NH_4Cl solution and diluted with ether. Ether-layer was separated, washed with brine (50 ml), dried over $MgSO_4$ and evaporated. The crude product was chromatographed over silica gel with CH_2Cl_2 and EtOAc as eluent (7:1) yielding pure product (5.5g, 46%) as an oil. ^1H NMR (300 MHz, $CDCl_3$) δ:2.30 (2H, m, CH_2 of dioxane acetal), 3.23 (1H, t, J=6.8 Hz, $CH_2O\underline{H}$), 3.78, 3.80 (3H, s, each, -OMe), 3.98 (2H, m, CH_2 of dioxane acetal), 4.26 (2H, dd, J=4.6, 11.3 Hz, CH_2 of dioxane acetal), 5.03 (2H, d, J=6.8 Hz, $C\underline{H}_2OH$), 6.21 (1H, s, methine proton of dioxane acetal), 6.77, 6.86 (1H, d each, J=10 Hz, Ar$\underline{H}$).

Step 2: 2,5-dimethoxy-6-mesyloxymethylbenzaldehyde dioxane acetal

To a solution of 2,5-dimethoxy-6-hydroxymethyl benzaldehyde dioxane acetal (19.8g, 78 mmol) in dry CH_2Cl_2 (225 ml) at 0°C was added triethylamine (22 ml, 156 mmol) and methanesulfonyl chloride (9 ml). The mixture was stirred at 0°C for 2 hours. Saturated NH_4Cl solution (50 ml) was slowly added. CH_2Cl_2 layer was separated, washed

with water (25 ml) and brine (25 ml) dried over $MgSO_4$, evaporated (25g, 96%). MP: 87-90°C, ^1H NMR (300 MHz, $CDCl_3$) δ:3.22 (3H, S, $-OSO_2Me$), 3.77, 3.80 (3H, s, each, OMe), 3.95 (2H, m, $C\underline{H}_2$ of dioxane acetal), 4.24 (2H, dd, J=4.6, 11.3 Hz, CH_2 of dioxane acetal), 5.77 (2H, s, $C\underline{H}_2$-OMS), 6.18 (1H, s, Methine proton of dioxane acetal), 6.88 (2H, tightly bored, aromatic), 2.35 (2H, m, CH_2 of dioxane acetal).

Step 3: **Methyl-2-(2'formyl-3',6'-dimethoxy benzyloxy)acetate**

A mixture of methyl glycolate (3.2 ml, 41 mmol) and sodium methoxide in methanol (4.37M solution, 7.3 ml, 32 mmol) was held at 50°C for 4.5 hours under nitrogen. Methanol was removed, and dry DMSO (5 ml) was added. The mixture was cooled to 10°C. The mesylate (4.9g, 14.9 mmol) from step 2 in DMSO (50 ml) was added slowly, and the mixture was stirred at room temperature overnight. Ice (~50g) was added and the mixture was extracted with ether (200 ml x 3), washed with water (30 ml), dried and evaporated. The residue was dissolved in ether (100 ml) and 50 ml 1N HCl was added. The mixture was stirred at room temperature for 1.5 hour. Ether layer was separated, washed with brine (20 ml), dried and evaporated. Crude product was chromatographed over silica gel (hexanes/ethyl acetate: 2:1 as eluent), yielding 1.89 of pure product (45%). (MP: 177-179°C). 1H NMR data (300 MHz, $CDCl_3$) δ3.73, 3.81, 3.84 (3H, s, each, OMe), 4.16 (2H, s, $C\underline{H}_2-CO_2CH_3$), 4.97 (2H, s, benzylic $C\underline{H}_2$), 6.94, 7.08 (1H, d, each, J=9.2 Hz, aromatic protons), 10.58 (1H, s, -CHO).

Step 4: 3,4-dihydro-5,8-dimethoxy-isochroman-3-yl-formic acid

A mixture of sodium (280 mg, 12.2 mmol) and dry toluene (15 ml) was heated to reflux under nitrogen. Methyl 2-(2'-formyl-3', 6'-dimethoxy benzyloxy) acetate (1.26g, 4.7 mmol) in toluene (15 ml) was added dropwise. The mixture was held under reflux for 5 hours, cooled, and then transferred slowly into methanol (10 ml). Methanol was removed. THF (25 ml) and 2N NaOH (25 ml) were added, the mixture was stirred for 1.5h at room temperature. THF was removed, extracted with CH_2Cl_2 (50 ml). Aqueous portion was acidified with dil. HCl, extracted with ethyl acetate (2x150 ml) washed with brine (25 ml) dried and evaporated. Crude product in CH_2Cl_2 (25 ml) was treated with p-toluenesulfonyl chloride (500 mg) pyridine (1 ml) overnight at 5°C. Product obtained after usual work-up was heated with pyridine (5 ml) at 120°C for 3 hours. The mixture was cooled diluted with water, neutralised with 3N HCl, extracted with ethyl acetate (3x50 ml). Solvent was removed and the product was dissolved in CH_2Cl_2 (50 ml). It was extracted with 10% $NaHCO_3$ (2x25 ml). The aqueous extract was acidified with dil. HCl, extracted with EtOAc (2x75 ml) washed with brine, dried and evaporated yielding fairly pure solid product (300 mg, 27%). NMR (300 MHz, $CDCl_3$) δ:3.77, 3.79 (3H, s, each, OMe), 5.26 (2H, s, benzylic $C\underline{H}_2$), 6.71, 6.77 (1H, d, each, J=9.1 Hz, aromatic proton), 7.32 (1H, s, olefinic proton).

Step 5: 5,8-dimethoxy-isochroman-3-yl-formic acid

To a solution of isochroman (5 mg, .02 mmol) in dry methanol (5 ml) magnesium turnings (10 small pieces) were

added gradually (one at a time) over 4 hours. The mixture was stirred overnight, acidified with dil. HCl. Methanol was removed and extracted with ether. Ether extract was washed with brine, dried and evaporated. The residue (1 mg) showed identical NMR spectrum as that of 5,8-dimethoxy-isochroman-3-yl-formic acid. (MP: 164-166°C).

Step 6: **Ethyl(1-formyl-trimethyleneacetal-3,6-dimethoxy) benzylthioacetate**

To a stirred solution of 2-bromomethyl-3,6-dimethoxyben- zaldehyde trimethylene acetal (650 mg, 2.05 mmol) were added a solution of 2-mercaptoacetate (0.25 ml, 2.28 mmol) in 2 ml of CH_3OH and a solution of NaOMe (4.37 M in CH_3OH, 0.47 ml, 2.05 mmol) at 0°C under argon. The resulting mixture was slowly warmed to room temperature and stirred for 6 hours. 20 ml of H_2O and 100 ml of Et_2O were added. The aqueous layer was extracted with ether (3x20 ml). The combined organic layers were washed with H_2O, dried over $MgSO_4$, filtered and then concentrated to a residue which was found to be almost pure title product and used for next reaction without further purification.

Step 7: **Methyl(1-formyl-3,6-dimethoxy)benzylthioacetate**

The reaction residue from step 6 above was dissolved in 20 ml of ether and 15 ml of 1N HCl solution. After stirred at room temperature for 2 hours, the organic layer was separated, washed with 5% $NaHCO_3$ solution, dried,

filtered and then concentrated. Flash chromatography of the residue with hexane and ethyl acetate (7:3) provided title product (474 mg, 1.67 mmol) in 81% overall yield for two steps. ^{1}H NMR ($CDCl_3$) δ: 3.32 (s, 2H), 3.72 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.29 (s, 2H), 6.89 (1H, d, J=9.0 Hz), 7.08 (1H, d, J=9.0 Hz), 10.60 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 26.45, 34.47, 52.57, 56.54, 56.70, 111.46, 117.70, 123.71, 130.34, 152.11, 157.96, 171.74, 193.12.

Step 8: **3,4-dihydro-3-carbmethoxy-5,8-dimethoxyisothiochroman**

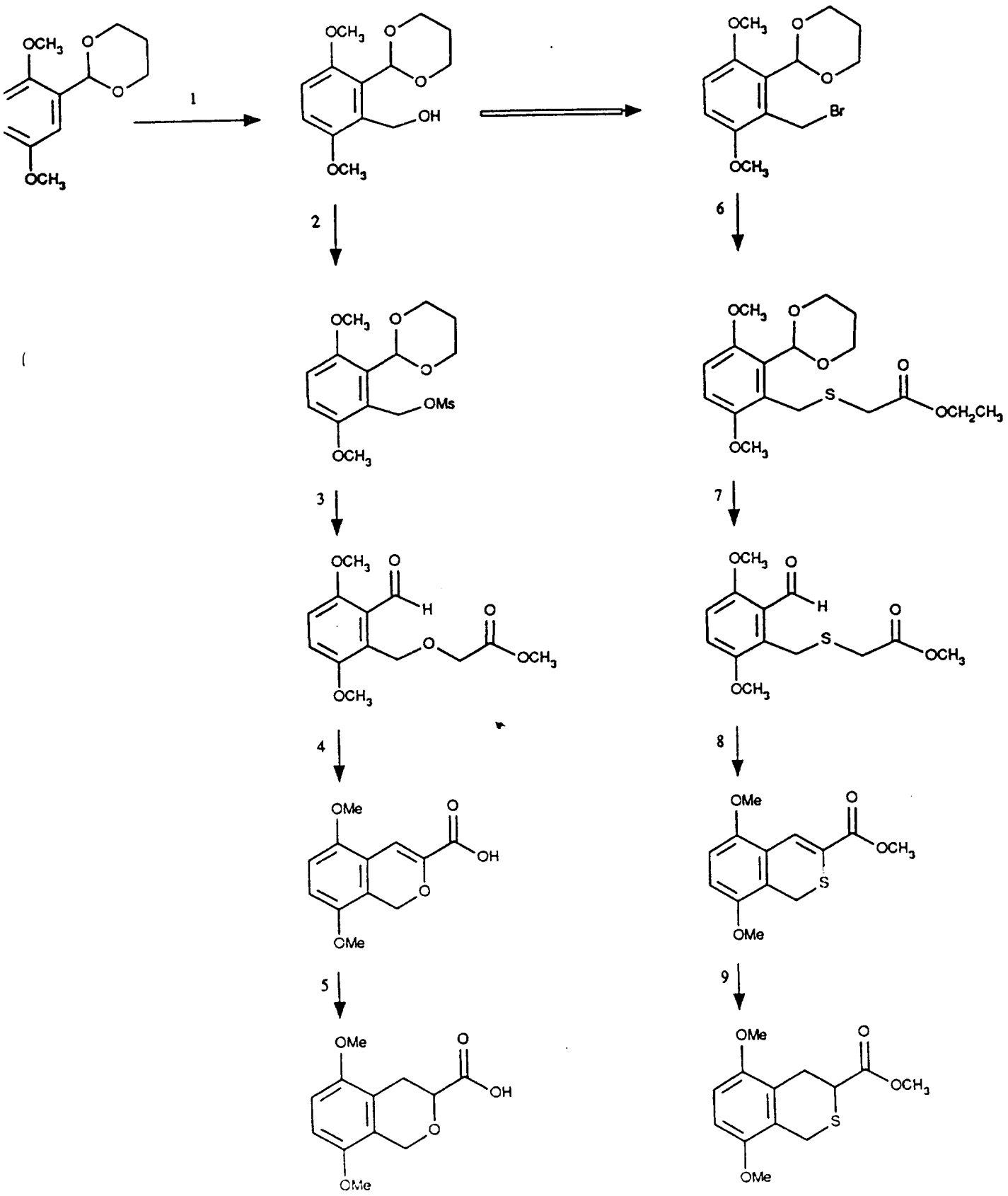
To a stirred solution of the aldehyde from step 7 above (400 mg, 1.4 mmol) in 30 ml of benzene was added NaOMe powder (152 mg, 2.8 mmol). The resulting mixture was heated to reflux for 3 hours. The solid was removed by filtration, washed with benzene. The filtrate was evaporated to a residue that was purified by flash chromatography to give the title compound (166.1 mg, 0.63 mmol) in 45% yield along with recovered starting material (83 mg, 20%). ^{1}H NMR ($CDCl_3$) δ: 3.82 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 3.94 (s, 2H), 6.73 (1H, d, J=9.0 Hz), 6.91 (1H, d, J=9.0 Hz), 8.14 (1H, s); ^{13}C NMR ($CDCl_3$) δ: 23.81, 52.74, 56.30, 56.47, 109.96, 114.13, 119.38, 123.36, 128.30, 128.97, 149.68, 151.45, 166.17.

Step 9: **3-carbmethoxy-5,8-dimethoxyisothiochroman**

To a stirred solution of the isothiochroman from step 8 above (129 mg, 0.48 mmol) in 20 ml of MeOH was added about 50 mg of magnesium chips. The reaction mixture started bubbling after 20 minutes induction period at room

temperature in water bath. Magnesium chips were added until all the starting material consumed. 10 ml of Nat. NH_4Cl solution, 10 ml of H_2O, and 50 ml of ether were added. The organic layer was separated, washed with H_2O, dried over $MgSO_4$, filtered and concentrated to a crude residue that was purified by flash chromatography to give the title compound (105 mg, 0.39 mmol) in 82% yield. The spectral data of title compound were found to be identical with the compound obtained in step 1, Example 8.

Example 12 : Alternative approaches to isochroman and isothiochroman derivatives



EXAMPLE 13:

Step 1: **2,5-dimethoxy-6-hydroxyethylbenzaldehydedioxane acetal**

To a cooled (-40°C) solution containing 1.68g (7.4 mmol) of 2,5-dimethoxybenzaldehydedioxane acetal in 50 ml of anhydrous diethylether was added, with stirring and under argon, 4.8 ml of a 2.5M n-butyl lithium in hexanes solution. The mixture was stirred for five hours at -5°C, 537 mg (6.0 mmol) of CuCN was then added, and stirring was continued for one more hour. To the mixture was then added 1.0g of ethylene oxide and stirred overnight at 4°C. The mixture was then washed with 20 ml of water, 20 ml of saturated aqueous sodium chloride and dried over $MgSO_4$. Flash chromatography of the residue obtained after removal of solvent gave 547mg (27% yield) of 2,5-dimethoxy-6-hydroxyethylbenzaldehyde dioxane acetal as a white solid. MP: 135-136°C. ^1H NMR (200 MHz, $CDCl_3$) δ:1.48 (bd, 1H, J=13.6 Hz, HC<u>He</u>), 2.32 (m, 1H, HC<u>Ha</u>), 3.48 (dt, 2H, J=4.76, 12.0 Hz, $ArCH_2$), 3.79 (s, 6H, $2XOCH_3$), 3.86-4.08 (overlapped m, 4H, 2XOHC<u>He</u> and CH_2OH), 4.29 (m, 2H, 2XOHC<u>Ha</u>), 6.28 (s, 1H, O-CH-O), 6.79 (dd, 2H, J=9.0 Hz, ArH). CMR (75.44 MHz, $CDCl_3$) δ: 25.9, 29.5, CH_2; 55.7, 56.3, OCH_3; 62.3, CH_2OH; 67.9, $2XOCH_2$; 97.6, O-CH-O; 109.5, 111.8, aryl CH; 126.3, 129.2, 150.8, 152.8, aryl C. IR (FT, $CDCl_3$) νMax: 3350, 3550, bs, OH; 1257, 1089, C-O. HRMS calculated for $C_{14}H_{20}O_5$: [$M^{+\cdot}$] 268.1311 found 268.1316.

Step 2: 5,8-Dimethoxy-1-hydroxyisochroman

A solution containing 150 mg (0.56mmol) of 2,5-dimethoxy-6- hydroxyethylbenzaldehydedioxane acetal in 5 ml of THF was stirred for one hour at room temperature with 5 ml of 0.2M aqueous HCl. The mixture was thendiluted with 25 ml of dichloromethane, washed successively with 25 ml aliquots of aqueous sodium bicarbonate, water, brine and then dried over $MgSO_4$. Flash chromatography of the residue obtained after removal of solvent gave 97 mg (82% yield) of the titled 1-hydroxyisochroman. (MP: 217°-219°C). ^1H NMR (200 MHz, $CDCl_3$) δ: 2.73 (m, 2H, CH_2), 3.09 (bs, 1H, exchangeable, OH), 3.84 (s, 3H, OCH_3), 3.88 (s, 3H, OCH_3), 4.03 (m, 1H, OHCH), 4.27 (m, 1H, OHCH), 6.12 (bs, 1H, OCH), 6.77 (dd, 2H, J=7.2 Hz, ArH). CMR (75.44 MHz, $CDCl_3$) δ: 22.2, CH_3; 55.5, 55.7, OCH_3; 56.8, OCH_2; 87.4, OCH; 107.9, 109.4, aryl CH; 124.2, 124.8, 150.4, 150.6, aryl C. IR (FT, $CDCl_3$) νMax: 3650, bs, OH; 1260, C-O. HRMS calculated for $C_{11}H_{14}O_4$: [$M^{+\cdot}$] 210.0892 found 210.0871.

Step 3: 1-Hydroxy-5,8-dioxo-5,8-dihydroisochroman

To a stirred solution containing 75 mg (0.36 mmol) of 5,8- dimethoxy-1-hydroxyisochroman from step 2 above in 2 ml of THF was added dropwise over four minutes, a solution containing 546 mg (1.0 mmol) of ceric ammonium nitrate in 2 ml of water. The mixture was stirred for five minutes and then diluted with 10 ml of dichlorome-thane. The separated organic phase was washed with 5 ml of water, 5 ml of brine and dried over $MgSO_4$. Following evaporation of solvent, the yellow oil (62 mg, 96% yield) was found to be pure isochromandione. 1H NMR (200 MHz, $CDCl_3$), δ: 2.54 (m, 2H, CH_2), 3.51 (d, 1H, J=4.4 Hz, exchangeable, OH), 4.09 (m,

2H, OCH_2), 5.88 (d, 1H, J=4.4 Hz, O-CH-O), 6.79 (dd, 2H, J=10.1 Hz, H-C=C-H). CMR (75.44 Mhz, $CDCl_3$) δ: 21.5, CH_2; 56.4, OCH_2; 85.3, OCH; 136.3, 136.4, aryl CH; 138.4, 141.3, CH; 185.3, 186.4, quinone C=O.

Step 4: **2,5-Dimethoxy-6-(2-hydroxypropyl)benzaldehydedioxane acetal**

Application of the procedure described in step 1 of this example gave 238mg (32% yield) of the desired benzaldehydedioxane acetal from 739mg (3.3 mmol) of 2,5-dimethoxybenzaldehydedioxane acetal and excess propylene oxide, after flash chromatography from 5% ethyl acetate in toluene. (MP: 160°-161°C). ^1H NMR (300 MHz, $CDCl_3$) δ: 1.33 (d, 3H, J=6.1 Hz, CH_3), 1.49 (bd, 1H, J=13.7 Hz, HC<u>He</u>), 2.30 (m, 1H, HC<u>Ha</u>), 3.10 (dd, 1H, J=2.4, 14.1 Hz, H<u>CH</u>), 3.47 (dd, 1H, J=9.5, 13.9 Hz, <u>H</u>CH), 3.78 (s, 6H, OCH_3), 4.02 (overlapped m, 3H, HO-C<u>H</u> and 2XHC<u>He</u>-O), 4.30 (m, 2H, $2XCH_2$-O), 6.27 (s, 1H, O-CH-O), 6.78 (dd, 2H, J=9.0 Hz, ArH). CMR (75.44 MHz, $CDCl_3$) δ: 25.1, CH_3; 25.8, 35.7, CH_2; 55.6, 56.3, OCH_3; 67.5, CHOH; 67.6, 67.7, OCH_2; 97.4, O-CH-O; 109.4, 111.7, aryl CH; 125.9, 129.3, 150.7, 152.7, aryl C. HRMS calculated for $C_{15}H_{22}O_5$: [$M^{+\cdot}$] 282.1467 found 282.1449. IR (FT, $CDCl_3$) νMax: 3300-3550, bs, OH; 1257, 1094, C-O.

Step 5: **5,8-Dimethoxy-1-hydroxy-3-methylisochroman**

Application of the procedure described in step 2 of this example gave 215 mg (86% yield) of the 3-methyl substituted isochroman from 250 mg of 2,5-dimethoxy-6-(2-

hydroxypropyl) benzaldehydedioxane acetal after flash chromatography with 20% ethyl acetate in hexanes. (MP: 240°-241°C). ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.41 (d, 3H, J=6.2 Hz, CH_3), 2.34 (dd, 1H, J=11.4, 17.4 Hz, HCHa), 2.81 (dd, 1H, J=3.25, 17.3Hz, HCHe), 3.02 (d, 1H, exchangeable, J=3.4 Hz, OH), 3.81 (s, 3H, OCH_3), 3.85 (s, 3H, OCH_3), 4.37 (m, 1H, OCH), 6.12 (d, 1H, J=3.3 Hz, O-CH-O), 6.74 (dd, 2H, J=8.9 Hz, ArH). CMR (75.44 MHz, $CDCl_3$): 21.3, CH_3; 29.8, CH_2; 55.7, 55.8, OCH_3; 62.6, O-CH; 88.6, O-CH-O; 107.9, 109.5, aryl CH; 124.6, 150.47, 150.53, aryl C. IR (FT, $CDCl_3$) νMax: 3630, bs, OH; 1260, C-O. HRMS calculated for $C_{12}H_{16}O_4$: [$M^{+\cdot}$] 224.1049 found 224.1036.

Step 6: **1-Hydroxy-5,8-dioxo-3-methyl-5,8-dihydroisochroman**

Oxidative demethyllation of 336 mg (1.5 mmol) of 5,8-dimethoxy-1- hydroxy-3-methylisochroman with 2.94 g (5 mmol) of ceric ammonium nitrate as described in step 3 of this example gave 262 mg (90% yield) of isochromandione as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.38 (d, 3H, J=6.3 Hz, CH_3), 2.15 (ddd, 1H, J=1.2, 11.0, 19.5 Hz, HCHa), 2.62 (dd, 1H, J=3.3, 19.5 Hz, HCHe), 3.16 (d, 1H, J=4.3 Hz, exchangeable, OH), 4.31 (m, 1H, O-CHCH$_3$), 5.91 (d, 1H, J=4.3 Hz, O-CH-O), 6.78 (dd, 2H, J=10.2 Hz, ArH).

Step 7: 1,2-oxiranebutane-3-one dioxane ketal

In a three neck, round bottom flask (29.776g, 0.35 mmol) 1,2-oxiranebutane-3-one, which had been previously

obtained following House's procedure (Organic synthesis Vol. III, p. 552), was mixed with 1,3-propanediol (118 ml, 1.59 mmol) and benzene (350 ml). To this mixture pyridinium tosylate was added (8.49g, 0.033 mmol). The mixture was refluxed, with water separation by a Dean-Stark trap, until the starting ketone has been completely used. The solution was washed twice with saturated sodium hydrogen carbonate solution, once with saturated sodium chloride solution, the organic phase was dried over sodium sulfate, and the bulk of the solvent was evaporated. The remaining mixture was distilled under reduced pressure to give the pure protected epoxy ketone in 22% yield. (BP: 20 mmHg, 75°C). ^{1}H NMR (300 MHz, $CDCl_3$) ppm: 1.28 (s, 3H, CH_3), 1.60 (multiplet, 2H, dioxane ring), 2.61 (dd, 1H, HCH-O-CH), 2.66 (dd, 1H, HCH-O-CH), 3.00 (t, 1H, HCH-O-C<u>H</u>), 3.91 (multiplet, 4H, dioxane ring). ^{13}C NMR (75.44 MHz, $CDCl_3$) ppm: 19.80 (CH_3, R_3C-CH_3), 25.42 (CH_2, $-O-CH_2-\underline{CH_2}-CH_2-O-$), 43.27 ($CH_2$, $\underline{CH_2}-O-CH-$), 56.46 (CH_2-O-CH), 60.84 (CH_2,-$O-\underline{CH_2}-CH_2-CH_2-O-$), 61.15 ($CH_2$, $-O-CH_2-CH_2-\underline{CH_2}-O-$), 96.65 (quaternary C, $CH_3C(O(CH_2)_3O)$. IR (FT, $CDCl_3$) cm^{-1}: 1494 (multiple bands, CH_2-O, oxirane ring. HRMS Clcd for $C_7H_{12}O_3$: $[M^{+\cdot}]$= 144.0786 found 144.0746.

<u>Step 8</u>: 1,4-dihydroxy-3-(ethane-1-one-dioxaneketal)-5,8-dimethoxy isochroman

A solution of 2.5M n-butyllithium (4.01 mmol) is added under argon at -15°C, to a stirred solution of 0.5g of 2,5-dimethoxy benzaldehyde dioxane acetal (2.23 mmol) in 20 ml of anhydrous ether and stirred for 5 hours at -7°C. At this point, 1.48 ml of BF_3 etherate (12.04 mmol) are added to 0.868g of 1,2-oxiranebu-tane-3-one dioxane ketal (6.02 mmol) at -78°C, with stirring. To this new mixture is added the lithio salt just formed. The reaction is left

stirring at -78°C overnight. Then the mixture is quenched with 20 ml of HH_4Cl sat. Ether is added and the phases are separated. The organic layer is washed twice with 75 ml of water. Once with NaCl sat. and dried over $MgSO_4$. Flash chromatography of the residue obtained gave the desired isochroman (13% yield). ^1H NMR (300 MHz, $CDCl_3$) ppm: 1.54 (s, 3H, CH_3), 1.58 (multiplet, 1H, -O-CH_2-HaCH-CH_2-O-), 1.88 (multiplet, 1H, -O-CH_2-HCHe-CH_2-O-), 2.71 (dd, 1H, HCH-CH(OH)), 2.78 (dd, 1H, HCH-CH-O), 3.76 (broad s, 6H, 2X O_3CH_3), 3.95 (multiplet, 4H, -O-CH_2-CH_2-CH_2-O-), 5.75 (s, 1H, dioxane ring), 6.70 (dd, 2H, ArH). ^{13}C NMR (75.44 MHz, $CDCl_3$) ppm: 21.53 (-C-CH_3) ppm: 21.53 (-C-CH_3), 25.33 (O-CH_2-CH_2-CH_2-O-), 55.66, 56.10 (O-CH_2-CH_2-CH_2-O-), 59.99 (CH_2-CH-O), 63.43, 68.21 (O-CH_3), 76.56 (CH_2-CH-O), 94.16 (CH-OH), 99.11 (C-quaternary, dioxane ring), 108.60, 109.86 (CH, aromatic). IR: (FT, $CDCl_3$) cm^{-1}: 3670 (OH).

Step 9: **1-hydroxy-3-(ethane-1-one dioxane ketal)-5,8-dioxo-5,8-dihydroisochroman**

A solution of 63.59g ceric ammonium nitrate ($1.16x10^{-4}$mmol) in 1 ml of H_2O is added dropwise to a stirred solution of 12 mg of 1-hydroxy-3-(ethane-1-one dioxane ketal)-5,8-dimethoxy isochroman (3.87×10^{-5}mmol) in 1 ml of acetonitrile, at room temperature. After 8 minutes, the mixture is diluted with 10 ml of CH_2Cl_2. The layers are separated. The aqueous layer is extracted twice with CH_2Cl_2 and the organic layers are washed twice with water, once with NaCl sat., and dried over $MgSO_4$. The residue obtained after evaporation of solvent gave a mixture of compounds including the desired quinone. IR: (FT, $CDCl_3$) cm^{-1}: 3600-3700 (broad OH), 1664.1 (C=O, stong band, quinone).

Step 10: **2,5-dimethoxy-6-(1-hydroxy-2,3-isopropylidenepropane) benzaldehyde dioxane acetal**

A solution of 2.5M n-butyllithium (4.014 mmol) is added under argon at -15°C, to a stirred solution of 0.5g of 2,5-dimethoxy benzaldehyde dioxane acetal (2.23 mmol) in 20 ml of anhydrous ether and stirred for 5 hours at -7°C. To this mixture is added 0.78g of isopropylidene-D-glyceraldehyde (6.02 mmol) at -78°C. Isopropyli-dene was previously prepared using David Y. Jackson's procedure (Synthetic Communications, 18(4), 337, 1988). The new mixture is warmed up to room temperature and left reacting overnight. Ether is added and the solution is washed twice with H_2O, once with NaCl sat., and dried over $MgSO_4$. Flash chromatography of the residue obtained after evaporation of the solvent gave the desired product. ^1H NMR (300 MHz, $CDCl_3$) ppm: 1.35 (multiplet, 1H, -O-CH_2-HaCH-CH_2-O-), 1.42 (broad s, 3H, CH_3), 1.50 (broad s, 3H, CH_3), 2.25 (multiplet, 1H, -O-CH_2-HCHe-CH_2-O-), 3.76, 3.79 (2 s, 6H, O-CH_3), 3.90 (multiplet, 4H, -O-CH_2-CH_2-CH_2-O-), 4.24 (2 dd, 2H, CH_2 group on isopropylidene), 4.85 (q, 1H, CH group on isopropylidene), 5.76 (t, 1H, -CH(OH)), 6.21 (s, 1H, dioxane ring) 6.81 (dd, 2H, aromatic). IR: (FT, neat) cm^{-1}: 3400 (OH, broad band). HRMS Clcd for $C_{18}H_{26}O_7$: $[m^{+\cdot}]$=354.1678 found 354,1670.

Step 11: **1,4-dihydroxy-3-hydroxymethyl-5,8-dimethoxy-isochroman**

Treatment of 2,5-dimethoxy-6-(1-hydroxy-2,3-isopropylidene-propane) benzaldehyde dioxaneacetal with

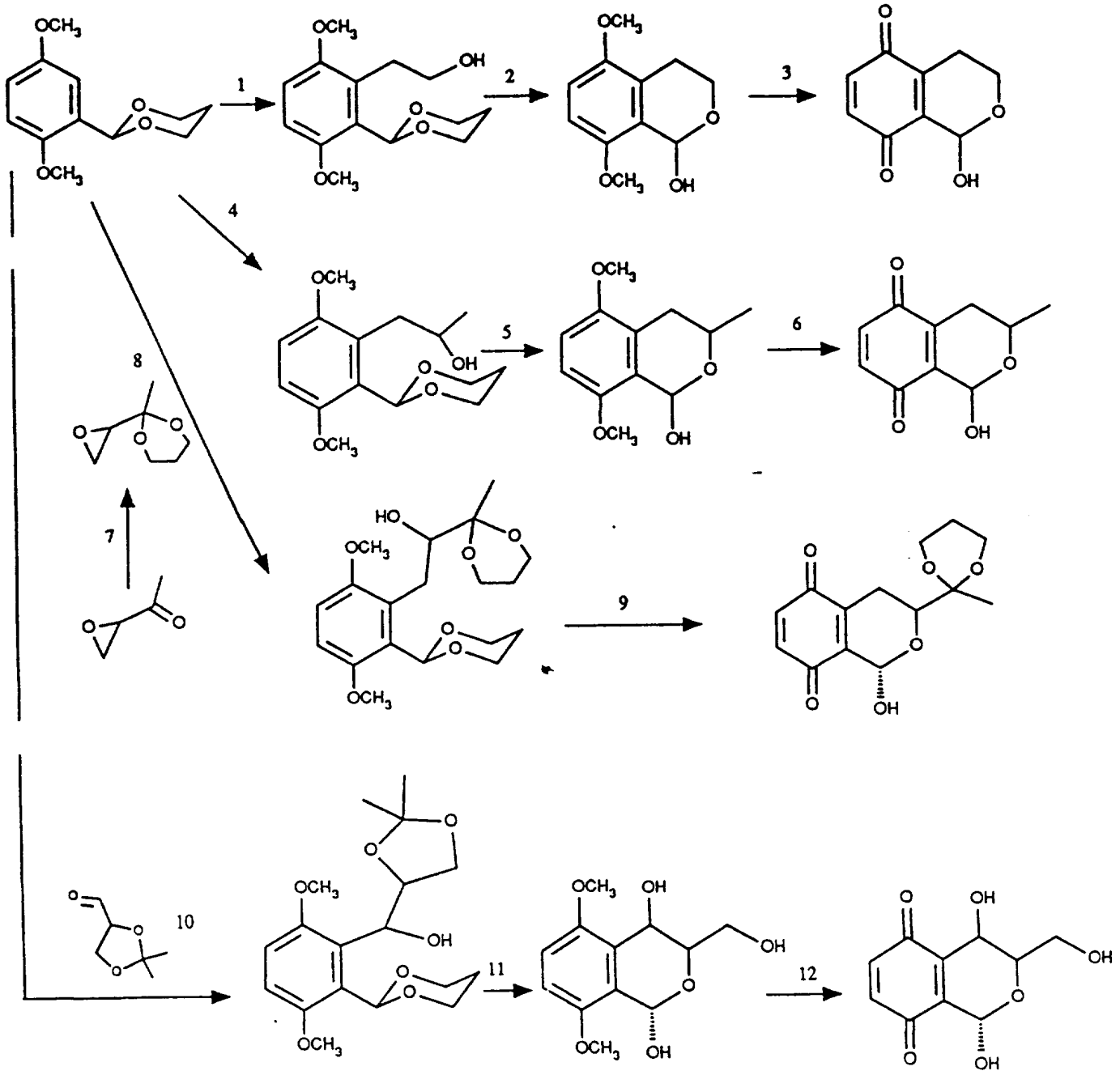
silica gel gave the desired isochroman (23% yield). ^1H NMR (300 MHz, $CDCl_3$) ppm: 3.48 (dd, 1H, CH(OH)-CH-HC-OH), 3.81, 3.86 (2 s, 6H, O-CH_3), 4.03 (t, 1H, -CH(OH)-CH-HCH-OH), 4.51 (broad d, 1H, -CH-(OH)-CH-CH_2OH), 4.89 (dd, 1H, (OH)CH-CH-CH_2OH), 6.50 (s, 1H, -CH-O-CH-CH_2OH), 6.81 (dd, 2H, aromatic). ^{13}C NMR (75.44 MHz, $CDCl_3$) ppm: 56.11 (-CH_2OH), 56.39 (OH)CH(O)-CH-CH_2OH), 63.64, 66.07 (2x-O-CH_3), 76.92 ((OH)CH-CH-CH_2OH), 95.13 ((OH)CH-O-CH-CH_2OH), 111.40, 11.75 (CH, aromatic), 122.02, 125.36 (C, aromatic; attached to pyranyl ring), 149.80, 152.36 (C, aromatic; bearing a methoxy group). IR: (FT, neat) cm^{-1}: 3520 (OH, not too intensed due to hydrogen bonding.) HRMS Clcd for $C_{12}H_{14}O_5$: ($M^{+\cdot}-H_2O$) = 238.0841 found 238.0871.

Step 12: **1,4-dihydroxy-3-hydroxymethyl-5,8-dioxo-3,4,5,8-tetrahydrobenzo (2,3c) pyran**

A solution of ceric ammonium nitrate ($1.40x10^{-4}$mmol) in 1 ml of H_2O is added dropwise to a stirred solution of 12 mg of 1,3-dihydroxy-3-hydroxymethyl-5,8-dimethoxy isochroman in 2 ml of acetonitrile, at room temperature. The reaction is followed by TLC; the product migrates at same height as the starting material, but is much more U.V. active than the starting material and therefore can be differentiated. After about 10 minutes of stirring, the reaction is over. CH_2Cl_2 (10 ml) is added, and the layers are separated. The aqueous layer is extracted twice with H_2O, once with NaCl sat., and dried over $MgSO_4$. The residue obtained after evaporation of the solvents gave the desired isochroman (628 yield) (MP: 138°-140°C). ^1H NMR (300 MHz, $CDCl_3$) ppm: 3.44 (dd, 1H, J=8.43, 2.08 Hz,

CH(OH)-CH-<u>CH</u>(OH)), 4.04 (dd, 1H, J=8.38, 6.70 Hz, CH(OHO-O-CH-<u>HC</u>H(OH)), 4.32 (broad s, 1H, -<u>CH</u>(OH)-CH-CH_2(OH)), 4.87 (ddd, 1H, J=6.55, 2.16, 1.21 Hz, (OH) CH-<u>CH</u>-CH_2(OH)), 6.20 (broad s, 1H, (OH)<u>CH</u>-O-CH-CH_2(OH)), 6.80 (dd, 2H, aromatic). IR: (FT, $CDCl_3$) cm^{-1}: 3600-3650 (OH, medium band), 1670.7 (C-O, quinone).

Example 13: Preparation of other key isochromandiones useful in the synthesis of various heteroanthracyclinones



EXAMPLE 14

Step 1: 5,12-dimethoxy-3-carbomethoxy-1,2,3,4-tetrahydro-(2-sulfur)-naphtacene-6,11-dione

1,4-Dimethoxy-2,3-dibromomethyl-anthraquinone (3.5g, 7.76 mmol) was dissolved in CH_2Cl_2/MeOH (300 ml, 6:4) followed by the addition of ethyl 2-mercaptoacetate (1,02 ml, 9.31 mmol) with stirring under argon. The mixture was then cooled to 0°C followed by dropwise addition of sodium methoxide (4.37M, 2.13 ml, 9.31 mmol). The reaction mixture was stirred for an additional 1h, and then concentrated in vacuo. The crude residue was redissolved in THF and cooled to 0°C, followed by the addition of NaOEt (0.63g, 9.31 mmol). The ice bath was then removed and the reaction was stirred until it had warmed to room temperature. The reaction mixture was then quenched with NH_4Cl, and extracted with CH_2Cl_2. The organic layers were combined, washed with H_2O, dried over $MgSO_4$ and concentrated in vacuo to give a residue which was flash chromatographed using hexane, EtOAc, and CH_2Cl_2 (5:1:6) giving the desired products (679 mg) in 22% yield. ^1H NMR (300 MHz, $CDCl_3$) δ: 1.28 (t, 3H, J=7.0 Hz), 3.17 (dd, 1H, J=16.62, 7.83, HCHa-C=O), 3.44 (dd, 1H, J=16.7, 5.5 Hz, HCHeCHC=O), 3.76, 3.77 (m, 2H, OCHC=O or HCHa-S), 3.78 (s, 6H, OCH_3), 3.99 (m, 1H, HCHe-S), 4.20 (q, 2H, J=7.0 Hz), 7.74 (m, 2H, ArH). 8.17 (m, 2H, ArH).

Step 2: 3-carbethoxy-5,12-dihydroxy-1,2,3,4-tetrahydro-(2-sulfur)-naphthacene-6,11-dione

To a stirred solution of I (20 mg, 0.05 mmol) in 5 ml of CH_2Cl_2 at -78°C was added dropwise BBr_3 (2.04 ml) under argon. The reaction mixture was stirred at -78°C for 1.5 hour before it was quenched with 5 ml of H_2O and 10 ml of CH_2Cl_2. The organic layer was separated, washed with H_2O, dried over $MgSO_4$, filtered and concentrated to residue which was found to be pure II (19 mg, 0.05 mmol, 100%). ^1H NMR ($CDCl_3$) δ: 1.29 (3H, t, J=7.0 Hz), 3.28 (2H, m), 3.90 (3H, m), 4.22 (2H, q, J=7.1 Hz), 7.80 (2H, m), 8.31 (2H, m), 13.49 (1H, s), 13.50 (1H, s), ^1H NMR (C_6D_6) δ:0.90 (3H, t, J=7.1 Hz), 3.08 (1H, m), 3.33 (1H, m), 3.42 (1H, m), 3.88 (4H, m), 7.85 (2H, m), 8.14 (2H, m), 13.78 (1H, s), 13.86 (1H, s), ^{13}C NMR ($CDCl_3$) δ: 14.13, 22.74, 26.11, 39.32, 61.74, 126.93, 133.48, 134.36, 155.10, 156.30, 168.01, 186.64.

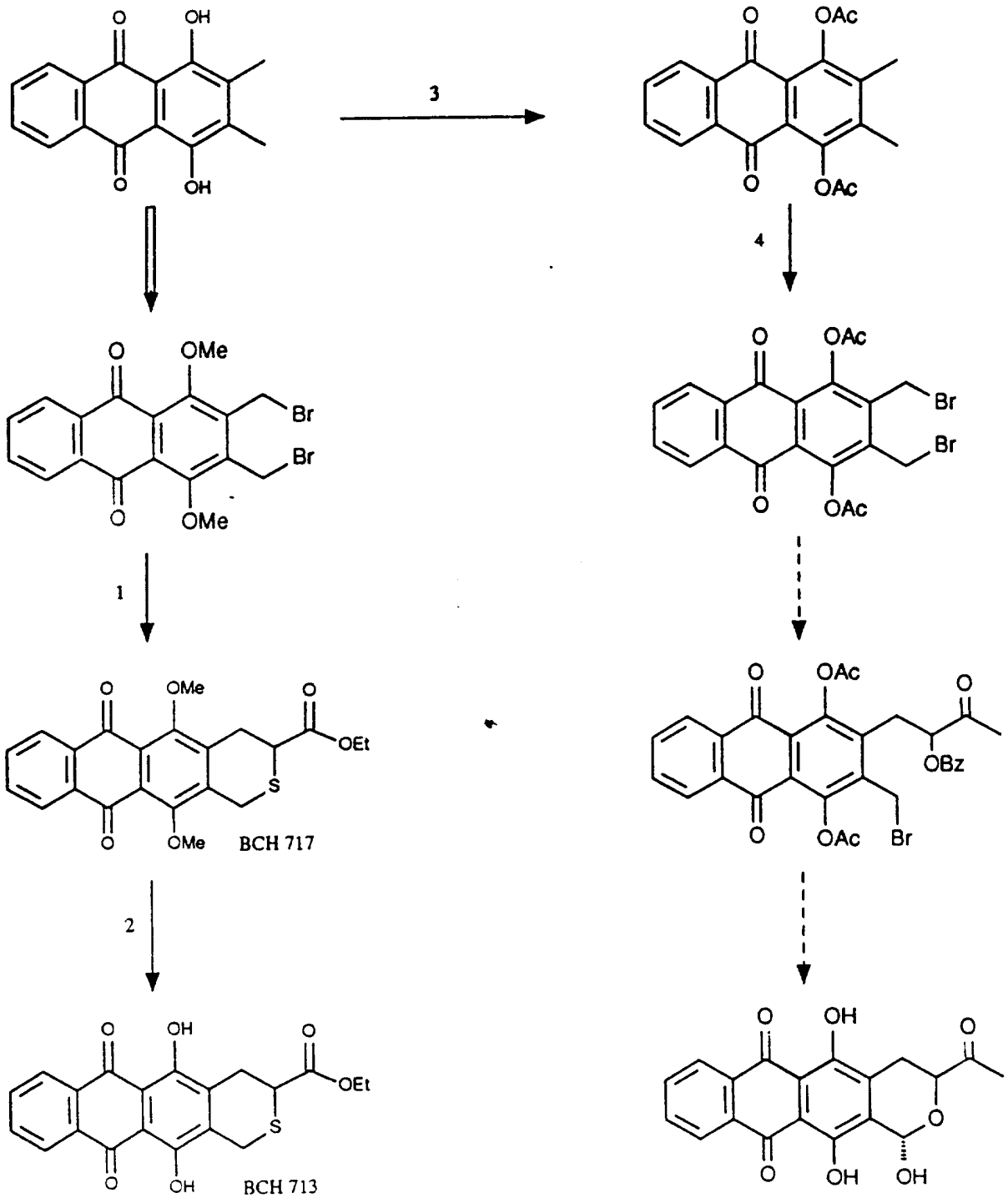
Step 3: 1,4-diacetyl-2,3-dimethylanthraquinone

To a stirred suspension of 2,3-dimethylquinizarin (5.00 g, 18.637 mmol) in dry CH_2Cl_2 (250 ml) was added acetic anhydride (40 ml) pyridine (40 ml) and dimethylaminopyridine (DMAP, 1.7g) at room temperature under argon. After two hours, the reaction mixture was poured into a mixture of ethyl acetate and ice (1:1, 800 ml), extracted with CH_2Cl_2, and the combined organic layers were dryed over $MgSO_4$. Flash chromatography with toluene and ethylacetate; (95.5%) gave 2.517g of pure compound (38% yield). (MP: 222-224°C). ^1H NMR ($CDCl_3$) δ: 2.27 (s, 6H, $\underline{CH_3}$, 2.53 (s, 6H, $CO\underline{CH_3}$), 7.72 (m, 2H, ArH), 8.15 (m, 2H, ArH).

Step 4: 1,4-diacetyl-2,3-bis-(bromomethyl)-anthraquinone

A mixture of diacetylated quinizarin from step 1 above, (2.221g, 8.801 mmol), NBS (3.956g, 22.002 mmol) and benzoyl peroxide (178 mg) in CCl_4 (350 ml) was refluxed and irradiated under argon with a 100W lamp for 5 hours. Additional NBS (0.5 mmol) and benzoyl peroxide (0.2 mmol) were added. Reflux was continued for 3 hours and the solution was then cooled. Evaporation of the solvent *in vacuo* followed by flash chromatography with toluene and ethylacetate (97.5%: 2.5%) gave 3.095g of the titled compound (88% yield). (MP: 225-227°C). ^1H NMR ($CDCl_3$) δ: 2.56 (s, 6H, $OCOCH_3$), 4.59 (br.s, 4H, CH_2Br), 7.75 (m, 2H, ArH), 8.14 (m, 2H, ArH).

Example 14: Preparation of pyrano and thiopyrano modified anthracyclinones from 2,3-dimethyl quinizarine



Example 15

Antitumor Activity

BCH-242 was subjected to an in vitro cytotoxicity evaluation against 57 tumor cell lines to assess its potential as an anticancer drug. These assays were carried out at the Developmental Therapeutics Program, Division of Cancer Treatment, National Cancer Institute (Bethesda, Maryland, U.S.A.). The method consists of incubating varying concentrations of the drug with an inoculum of cells for two days. At the end of the assay, the number of viable cells is estimated with a dye, sulforhodamine B. The protocol is described in M.R. Boyd, "Status of the NCI Preclinical Antitumor Drug Discovery Screen", Principles and Practices of Oncology, 3, pp. 1-12, 1989. The 57 cell lines included two mouse leukemia lines (P388 parental and adriamycin resistant) and 56 human cell lines.

There are three parameters calculated: GI_{50}, the log molar conc. of drug required to inhibit cell growth by 50%; TGI, the log molar conc. of drug required to completely block cell growth; LC_{50}, the log molar concentration of drug required to reduce the original cell number by 50%. It should be noted that the first two parameters (GI_{50} and TGI) relate to antiproliferation effects while the third one (LC_{50}) indicates true cytotoxicity. A value of -4 or greater is considered to denote resistance (inactivity). The results are presented in the Table below.

A number of interesting observations can be made regarding the activity profile of BCH-242. This analog is able to inhibit cell growth of both mouse leukemia cell lines (P388 parental and adriamycin resistant) to an equal

extent (-5.78 vs -5.63). Likewise, BCH-242 shows a similarcytotoxic effect against MCF-7 parental and adriamycin resistant lines (-5.27 vs -5.15). The ability of BCH-242 to show activity against cell lines having known drug resistance suggests that the compound may be acting by an advantageous mechanism and that the compound may be clinically useful.

In addition, the various human and mouse leukemia lines, although sensitive to the antiproliferative effect of BCH-242, display some resistance to the cytotoxic effect of the drug. However, most of the cell lines of solid tumors ultimately show cytotoxicity to the drug. Since the potency of drugs against experimental leukemia usually predicts clinical bone marrow toxicity, it suggests that BCH-242 might be active clinically against certain solid tumors while exhibiting a minimal myelotoxic effect.

ANTIPROLIFERATIVE AND CYTOTOXIC EFFECTS OF BCH-242 IN TUMOR CELL LINES

Panel/Cell Line	$Log_{10}GI50$	$Log_{10}TGI$	$Log_{10}LC50$
Leukemia			
CCRF-CEM	-5.83	-5.35	> -4.00
HL-60TB	-5.70	-5.30	> -4.00
K562	-5.72	-5.35	> -4.00
MOLT-4	-5.89	-5.49	-5.09
RPMI-8226	-5.77	-5.35	-4.47
Non-Small Cell Lung Cancer			
A-549	-5.51	-5.00	-4.42
EKVX	-5.75	-5.47	-5.20
HOP-18	-5.72	-5.31	-4.78
HOP-62	-5.25	-4.75	-4.37
HOP-92	-5.70	-5.43	-5.17
NCI-H226	-5.56	-5.18	-4.59
NCI-H23	-5.74	-5.49	-5.23
NCI-H322	-4.90	-4.53	-4.16
NCI-H460	-5.71	-5.40	-5.09
NCI-H522	-6.04	-5.68	-5.34
Small Cell Lung Cancer			
DMS-114	-5.80	-5.52	-5.24
DMS-273	-5.68	-5.35	-5.01
Colon Cancer			
COLO-205	-5.95	-5.63	-5.31
DLD-1	-5.80	-5.49	-5.17
HCC-2998	-5.63	-5.24	-4.72
HCT-15	-5.78	-5.45	-5.12
HT-29	-5.81	-5.45	-5.09
KM-12	-5.49	-4.97	-4.49
KM-20L2	-5.66	-5.27	-4.75
SW-620	-5.88	-5.54	-5.19
CNS Cancer			
SF-268	-5.31	-4.59	-4.40
SF-295	-5.62	-5.15	-4.59
SF-539	-5.69	-5.36	-5.03
SNB-19	-5.42	-4.88	-4.44
SNB-75	-5.53	-5.06	-4.52
SNB-78	-4.82	> -4.00	> -4.00
U-251	-5.60	-5.14	-4.59
XF-498 L	-5.79	-5.50	-5.22
Melanoma			
LOX-IMVI	-5.73	-5.49	-5.24
MALME-3M	-5.75	-5.49	-5.24
M19-MEL	-5.81	-5.51	-5.21
SK-MEL-2	-5.77	-5.51	-5.24
SK-MEL-28	-5.62	-5.37	-5.11
SK-MEL-5	-5.83	-5.55	-5.26
UACC-257	-5.70	-5.44	-5.18
UACC-62	-5.76	-5.50	-5.25
Ovarian Cancer			
IGROV-1	-5.75	-5.42	-5.10
OVCAR-3	-5.82	-5.52	-5.23
OVCAR-4	-5.74	-5.48	-5.22
OVCAR-5	-5.70	-5.46	-5.23
OVCAR-8	-5.49	-5.49	-5.19
SK-OV-3	-5.22	-4.77	-4.38
Renal Cancer			
A498	-4.86	-4.57	-4.28
CAKI-1	-5.52	-5.12	-4.59
RXF-393L	-5.89	-5.58	-5.27
SN-12C	-5.79	-5.52	-5.26
SN12K1	-5.48	-5.12	-4.60
UO-31	-5.62	-5.25	-4.77
Miscellaneous			
MCF-7	-5.81	-5.54	-5.27
MCF-7/ADR	-5.76	-5.46	-5.15
P388	-5.78		> -4.00
P388/ADR	-5.63	-4.99	-4.16
Mean	-5.65	-5.28	-4.84

Example 16

In Vitro Clonogenic Assays of Heteroanthracyclines

A series of heteroanthracycline analogs were evaluated by the NCI at Bethesda, Maryland, USA. The same protocol as described in example 15 for BCH-242 was used. Tables 1 and 2 summarise the GI_{50} and LC_{50} average values obtained from a group of cell lines, per type of cancer. The original NCI data for the various derivatives, is provided herein in tables 3 to 11.

With reference to table 1, the heteroanthracycline derivatives show a weaker antiproliferative activity than daunomycin (DNM) or adriamycin (ADR) in the different type of cancers. However, the ability of the heteroanthracycline agents to kill the solid tumor cells is clearly denoted in Table 2. Cytotoxycity ranges from a mean potency of -4.09 in BCH-674 to as high as -5.32 in BCH-242 in solid tumors. Most notably is the fact that average cytotoxicity in leukemia is generally much lower than with DNM or ADR. This is a desirable feature and may indicate a lower bone marrow toxicity than with the clinical agents, DNM and ADR. Since myelotoxicity limits the single dosage that can be administered to a patient, these results suggest that higher and more therapeutically useful single dosages would be permissible with the heteroanthracyclines of this invention in the chemotherapy against solid tumors.

TABLE 1

Average LOG $_{10}$ GI $_{50}$ Multiple cell lines

BCH no.	Leukemia	NSC lung	SC lung	Colon	CNS	Melanoma	Ovarian	Renal	Mean Potency in solid tumors
DNM	-7.25±0.10	-7.04±0.23	-7.14±0.01	-6.82±0.31	-7.04±0.15	-6.95±0.21	-6.86±0.18	-6.79±0.47	-6.95±0.22
ADR	-7.51±0.52	-7.33±0.76	-7.27±0.12	-6.61±0.35	-7.07±0.26	-6.92±0.26	-6.55±0.19	-6.74±0.41	-6.93±0.29
242	-6.50±0.14	-6.01±0.34	-6.45±0.26	-6.50±0.32	-5.81±0.23	-6.36±0.41	-6.13±0.41	-6.02±0.22	-6.18±0.24
670	-5.78±0.10	-5.51±0.32	-5.48±0.23	-5.69±0.17	-5.44±0.30	-5.75±0.12	-5.42±0.40	-5.36±0.35	-5.52±0.13
671	-5.74±0.05	-5.34±0.38	-5.60±0.06	-5.72±0.05	-5.37±0.19	-5.68±0.09	-5.44±0.35	-5.55±0.14	-5.53±0.14
672	-5.89±0.09	-5.45±0.29	-5.69±0.14	-5.78±0.18	-5.33±0.25	-5.81±0.14	-5.50±0.35	-5.38±0.26	-5.56±0.18
673	-5.97±0.06	-5.76±0.36	-5.74±0.00	-6.10±0.32	-5.65±0.06	-5.83±0.05	-5.81±0.26	-5.80±0.09	-5.81±0.13
674	-5.06±0.14	-5.03±0.38(1R)	-4.88±0.14	-4.87±0.29	-4.86±0.07(1R)*	-4.88±0.12	-4.80±0.09	-5.05±0.27	-4.91±0.09
675	-5.53±0.11	-5.03±0.33	-5.14±0.22	-5.06±0.24	-4.97±0.19(1R)	-5.23±0.23	-5.07±0.28	-5.04±0.30	-5.08±0.08
681	-5.69±0.05	-5.54±0.28	-5.77±0.04	-5.85±0.21	-5.54±0.15	-5.95±0.29	-5.57±0.12	-5.52±0.27	-5.68±0.16
683	-5.74±0.03	-5.52±0.23	-5.73±0.01	-5.89±0.24	-5.47±0.17	-5.95±0.25	-5.68±0.12	-5.50±0.29	-5.68±0.18
689	-4.81±0.04	-4.87±0.13	-4.94±0.02	-4.95±0.05	-4.89±0.10	-4.90±0.05	-4.94±0.05	-4.950.04	-4.92±0.03

* Represents the number of cell lines which are considered to be refractory towards the compound's cytotoxicity (Log $_{10}$ GI $_{50}$ <-4.00).

TABLE 2

Average LOG $_{10}$ LC $_{50}$ Multiple cell lines

BCH no.	Leukemia	NSC lung	SC lung	Colon	CNS	Melanoma	Ovarian	Renal	Mean Potency in solid tumors
DNM	-4.30±0.36	-5.07±0.37	-5.58±0.09	-4.83±0.37	-5.08±0.42	-5.64±0.17	-4.78±0.20	-4.78±0.46	-5.11±0.34
ADR	-4.76±0.10	-5.01±0.26	-5.39±0.18	-4.86±0.27	-5.03±0.35	-5.56±0.29	-4.74±0.05	-4.87±0.38	-5.07±0.28
242	>-4.00	-5.21±0.38	-5.58±0.27	-5.59±0.36	-4.86±0.24	-5.41±0.07	-5.35±0.19	-5.22±0.21	-5.32±0.20
670	>-4.00	-4.62±0.27(1R)*	-4.41(1R)	-4.60±0.29(2R)	-4.58±0.15	-4.69±0.29(1R)	-4.40±0.13	-4.53±0.16	-4.57±0.09
671	>-4.00	-4.52±0.41	-4.26±0.20	-4.80±0.50(1R)	-4.37±.24	-4.67±0.57	-4.47±0.35	-4.63±0.24	-4.53±0.17
672	-4.37±0.15	-4.56±0.08	-4.40±0.20	-4.55±0.18	-4.50±0.16	-4.67±0.18	-4.59±0.13	-4.62±0.08	-4.56±0.08
673	>-4.00	-4.66±0.43	-4.44±0.04	-4.46±0.45	-4.57±0.22	-4.87±0.50	-4.66±0.50	-4.96±0.32	-4.66±0.18
674	>-4.00	-4.16±0.10	-3.92±0.14	-4.01±0.27	-4.20±0.06	-4.05±0.17	-4.08±0.17	4.24±0.14	-4.09±0.11
675	>-4.00	-4.25±0.23	-4.21±0.04	-4.07±0.22	-4.21±0.11	-4.10±0.23	-4.20±0.16	-4.25±0.10	-4.18±0.07
681	<-4.00	-4.64±0.41	-5.18	-5.14±0.27	-4.65(1)±0.24	-5.30±0.12	-4.78±0.18	-4.66(1)±0.40	-4.91±0.27
683	<-4.00	-4.55±0.42	-5.08	-4.98(1)±0.38	4.50(1)±0.21	5.15±0.22	-4.80±0.33	-4.58±0.36	-4.81±0.25
689	<-4.00	-4.38(±0.06)3R	-4.37(±0.05)	-4.41(±0.03)	-4.39(±0.05)2R	-4.38(±0.04)	-4.37(±0.07)	-4.43(±0.01)2R	-4.39(±0.02)

*Represents the number of cell lines which are considered to be refractory towards the compound's cytotoxicity (LOG $_{10}$ LC $_{50}$ <-4.00).

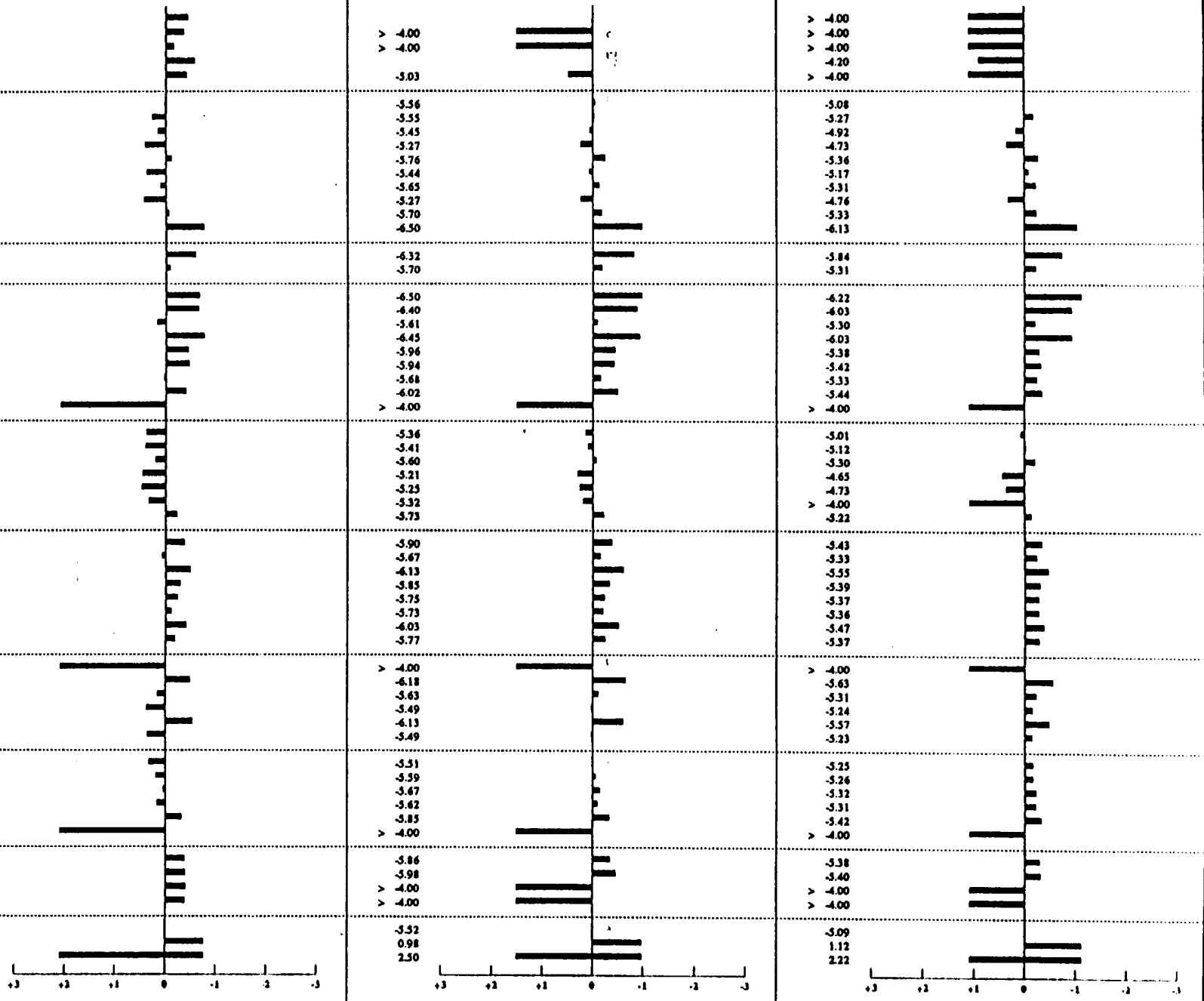
National Cancer Institute Developmental Therapeutics Program

TABLE 3 **Mean Graphs** BCH-242

NSC: D- 627446-P/ 1 | Units: Molar | SSPL: Y71X | Exp. ID: 8910NS76

Report Date: July 10, 1990 | **Test Date:** November 7, 1989

Panel/Cell Line	Log_{10} GI50	Log_{10} TGI	Log_{10} LC50
Leukemia			
CCRF-CEM	-6.55		> -4.00
HL-60 TB	-6.46	> -4.00	> -4.00
K-562	-6.26	> -4.00	> -4.00
MOLT-4	-6.69		-4.20
RPMI-8226	-6.52	-5.03	> -4.00
Non-Small Cell Lung Cancer			
A-549	-6.09	-5.36	-5.08
EKVX	-5.83	-5.55	-5.27
HOP-18	-5.94	-5.45	-4.92
HOP-62	-5.69	-5.27	-4.73
HOP-92	-6.21	-5.76	-5.36
NCI-H226	-5.71	-5.44	-5.17
NCI-H23	-5.99	-5.65	-5.31
NCI-H322	-5.67	-5.27	-4.76
NCI-H460	-6.16	-5.70	-5.33
NCI-H522	-6.87	-6.50	-6.13
Small Cell Lung Cancer			
DMS 114	-6.71	-6.32	-5.84
DMS 273	-6.19	-5.70	-5.31
Colon Cancer			
COLO-205	-6.79	-6.50	-6.22
DLD-1	-6.77	-6.40	-6.03
HCC-2998	-5.92	-5.61	-5.30
HCT-116	-6.88	-6.45	-6.03
HCT-15	-6.56	-5.96	-5.38
HT-29	-6.57	-5.94	-5.42
KM-12	-6.07	-5.68	-5.33
KM-20L2	-6.51	-6.02	-5.44
SW-620	> -4.00	> -4.00	> -4.00
CNS Cancer			
SF-268	-5.72	-5.36	-5.01
SF-295	-5.70	-5.41	-5.12
SF-539	-5.90	-5.60	-5.30
SNB-19	-5.64	-5.21	-4.65
SNB-75	-5.63	-5.25	-4.73
SNB-78	-5.76	-5.32	> -4.00
U-251	-6.33	-5.73	-5.22
Melanoma			
LOX-IMVI	-6.48	-5.90	-5.43
MALME-3M	-6.02	-5.67	-5.33
M19-MEL	-6.60	-6.13	-5.55
SK-MEL-2	-6.40	-5.85	-5.39
SK-MEL-28	-6.33	-5.75	-5.37
SK-MEL-5	-6.22	-5.73	-5.36
UACC-257	-6.51	-6.03	-5.47
UACC-62	-6.29	-5.77	-5.37
Ovarian Cancer			
IGROV-1	> -4.00	> -4.00	> -4.00
OVCAR-3	-6.60	-6.18	-5.63
OVCAR-4	-5.94	-5.63	-5.31
OVCAR-5	-5.73	-5.49	-5.24
OVCAR-8	-6.65	-6.13	-5.57
SK-OV-3	-5.75	-5.49	-5.23
Renal Cancer			
A498	-5.78	-5.51	-5.25
CAKI-1	-5.91	-5.59	-5.26
RXF-393 L	-6.05	-5.67	-5.32
SN-12C	-5.94	-5.62	-5.31
SN-12K1	-6.42	-5.85	-5.42
UO-31	> -4.00	> -4.00	> -4.00
Miscellaneous			
MCF-7	-6.49	-5.86	-5.38
MCF-7/ADR	-6.50	-5.98	-5.40
P388	-6.51	> -4.00	> -4.00
P388/ADR	-6.49	> -4.00	> -4.00
MG_MID	-6.10	-5.52	-5.09
Delta	0.77	0.98	1.12
Range	2.88	2.50	2.22



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BAD ORIGINAL

National Cancer Institute Developmental Therapeutics Program

TABLE 4 **Mean Graphs** BCH-670

Report Date: N ember 26, 1990 | Test Date: October 22, 1990

Panel Cell Line	Log_{10} GI50	GI50	Log_{10} TGI	TGI	Log_{10} LC50	LC50
Leukemia						
CCRF-CEM	-5.85		-5.33		> -4.15	
HL-60(TB)	-5.81		-5.35		> -4.15	
K-562	-5.61		> -4.15		> -4.15	
MOLT-4	-5.75		-5.28		> -4.15	
RPMI-8226	-5.89		-5.31		> -4.15	
SR-SCID						
Non-Small Cell Lung Cancer						
A549/ATCC	-5.17		-4.76		-4.36	
EKVX	-5.64		-5.08		-4.60	
HOP-18	-4.99		-4.70		-4.41	
HOP-62						
HOP-92					-4.61	
NCI-H226	-5.65		-5.16		> -5.15	
NCI-H23	-5.56		> -5.15		-4.66	
NCI-H322M	-5.67		-5.18		-4.42	
NCI-H460	-5.14		-4.78		-5.27	
NCI-H522	-6.08		-5.67		-4.59	
EKVX-5291	-5.68		-5.08			
Small Cell Lung Cancer						
DMS-114	-5.71		-5.19		> -4.15	
DMS-273	-5.25		-4.80		-4.41	
Colon Cancer						
COLO-205	-5.76		-5.04		> -4.15	
HCC-2998	-5.72		-5.16		-4.60	
HCT-116	-5.92		-5.54		-5.17	
HCT-15	-5.72		-5.12		-4.26	
HT-29	-5.68		-5.09		-4.33	
KM-12	-5.29		-4.55		> -4.15	
KM20L-2	-5.67		-5.11		-4.59	
SW-620	-5.79		-5.41		-4.67	
CNS Cancer						
SF-268	-5.69		-5.15		> -5.15	
SF-295	-5.26		-4.85		-4.50	
SF-539	-5.50		-5.00		-4.57	
SNB-19	-5.05		-4.75		-4.44	
SNB-75	-5.44		-4.93		-4.53	
SNB-78	-5.85		-5.47		-4.84	
U251	-4.99		-4.70		-4.42	
XF-498	-5.72		-5.33		-4.79	
Melanoma						
LOX IMVI	-5.67		-5.15		-4.26	
MALME-3M	-5.85		-5.46		-4.94	
M14	-5.82		-5.42		-4.89	
MDA-MB-435	-5.74		-5.38		-4.71	
SK-MEL-2	-5.88		-5.29		-4.68	
SK-MEL-28	-5.50		-4.94		-4.52	
SK-MEL-5	-5.88		-5.53		-5.18	
UACC-257	-5.69		-5.17		-4.33	
UACC-62	-5.69		-5.24		> -4.15	
Ovarian Cancer						
IGROV1	-5.60		-5.09		-4.21	
OVCAR-3	-5.62		-5.03		-4.47	
OVCAR-4	-5.73		-5.15		-4.63	
OVCAR-5	-4.92		-4.66		-4.41	
OVCAR-8	-5.81		-5.35		-4.35	
SK-OV-3	-4.81		-4.58		-4.35	
Renal Cancer						
786-0	-5.76		-5.21		-4.57	
A498	-5.28		-4.86		-4.50	
ACHN	-4.99		-4.71		-4.43	
CAKI-1	-5.75		-5.29		-4.74	
RXF-393	-5.36		-4.84		-4.44	
RXF-631	-5.80		-5.38		-4.82	
SN12C	-4.81		-4.55		-4.29	
TK-10	-5.13		-4.80		-4.48	
UO-31						
Prostate Cancer	-5.56		-5.08		-4.53	
Breast Cancer	0.52		0.60		0.74	
MG_MID	1.27		1.52		1.13	

TABLE 5 **Mean Graphs** - BCH-671 | **Report Date:** November 26, 1990 | **Test Date:** October 22, 1990

Panel/Cell Line	Log_{10} GI50	GI50	Log_{10} TGI	TGI	Log_{10} LC50	LC50
Leukemia						
CCRF-CEM	-5.79		-5.29		> -4.00	
HL-60(TB)						
K-562	-5.67		-5.17		> -4.00	
MOLT-4	-5.70		-5.31		> -4.00	
RPMI-8226	-5.79		-5.34		> -4.00	
SR-WIU						
Non-Small Cell Lung Cancer						
A549/ATCC	-4.94		-4.56		-4.18	
EKVX	-5.65		-5.25		-4.64	
HOP-18	-4.84		-4.56		-4.28	
HOP-62						
HOP-92						
NCI-H226	-4.86		-4.54		-4.22	
NCI-H23	-5.39		-4.74		-4.09	
NCI-H460	-5.48		-4.92		-4.40	
NCI-H522	-5.78		-5.43		-5.09	
LXFL-529L	-5.79		-5.51		-5.24	
Small Cell Lung Cancer						
DMS 114	-5.67		-5.13		-4.05	
DMS 273	-5.54		-5.10		-4.46	
Colon Cancer						
COLO 205	-5.70		-5.31		> -4.00	
DLD-1	-5.79		-5.43		-5.06	
HCC-2998						
HCT-116	-5.80		-5.52		-5.25	
HCT-15	-5.69		-5.19		> -4.00	
HT29	-5.69		-5.36		-5.03	
KM12	-5.74		-5.37		-5.00	
KM20L2	-5.63		-5.12		-4.52	
SW-620	-5.69		-5.38		-5.07	
CNS Cancer						
SF-268	-5.49		-4.87		-4.19	
SF-295	-5.14		-4.63		-4.18	
SF-539	-5.59		-5.14		-4.60	
SNB-19	-5.19		-4.67		-4.26	
SNB-75	-5.37		-4.89		-4.42	
SNB-78	-5.49		-5.00		-4.09	
U251	-5.09		-4.68		-4.34	
XF 498	-5.60		-5.27		-4.86	
Melanoma						
LOX IMVI	-5.49		-4.90		> -4.00	
MALME-3M	-5.76		-5.47		-5.19	
M14	-5.79		-5.49		-5.19	
M19-MEL	-5.76		-5.43		-5.11	
SK-MEL-2	-5.66		-5.29		-4.77	
SK-MEL-28	-5.68		-5.27		-4.71	
SK-MEL-5	-5.57		-5.18		-4.61	
UACC-257	-5.72		-5.37		-5.02	
UACC-62	-5.68		-5.18		-4.01	
Ovarian Cancer						
IGROV1	-5.55		-5.04		-4.09	
OVCAR-3	-5.75		-5.02		-4.51	
OVCAR-4	-5.71		-5.46		-5.20	
OVCAR-5	-5.14		-4.70		-4.34	
OVCAR-8	-5.68		-5.22		-4.43	
SK-OV-3	-4.81		-4.53		-4.24	
Renal Cancer						
786-0	-5.66		-5.27		-4.74	
ACHN	-5.69		-5.29		-4.79	
CAKI-1	-5.41		-4.86		-4.42	
RXF-393	-5.71		-5.37		-5.03	
RXF-631	-5.34		-4.75		-4.24	
SN12C	-5.67		-5.30		-4.80	
TK-10	-5.42		-5.06		-4.54	
UO-31	-5.49		-4.88		-4.44	
MG_MID	-5.54		-5.11		-4.53	
Delta	0.25		0.41		0.72	
Range	0.99		1.00		1.25	

+3 +2 +1 0 -1 -2 -3

TABLE 6 **Mean Graphs** BCH-6775 **Report Date:** December 6, 1990 **Test Date:** October 22, 1990

Panel/Cell Line	Log_{10} GI50	Log_{10} TGI	Log_{10} LC50
Leukemia			
CCRF-CEM	-6.05	-5.36	> -4.12
HL-60(TB)		-5.24	> -4.12
K-562	-5.89	-5.56	-5.16
MOLT-4	-5.96	-5.48	> -4.12
RPMI-8226	-5.97		
SR-WIU			
Non-Small Cell Lung Cancer		-5.11	-4.29
A549/ATCC	-5.59	-5.41	-5.11
EKVX	-5.70	-4.85	-4.48
HOP-18	-5.36		
HOP-62		-5.48	-5.15
HOP-92	-5.81	-5.24	-4.46
NCI-H226	-5.74	-4.78	> -4.12
NCI-H23	-5.45	-5.15	-4.36
NCI-H460	-5.63	-6.11	
NCI-H522	-6.67	-5.60	-5.30
LXFL-529L	-5.91		
Small Cell Lung Cancer		-5.18	-4.40
DMS 114	-5.74	-5.36	-4.48
DMS 273	-5.74		
Colon Cancer		-5.47	> -4.12
COLO 205	-5.87	-5.36	-4.56
DLD-1	-5.82		
HCC-2998		-5.91	-5.30
HCT-116	-6.53	-5.28	> -4.12
HCT-15	-6.33	-5.40	-4.53
HT29	-6.42	-5.06	> -4.12
KM12	-5.68	-5.33	> -4.12
KM20L2	-5.79	-5.69	-4.84
SW-620	-6.36		
CNS Cancer		-5.00	-4.31
SF-268	-5.60	-5.07	-4.49
SF-295	-5.64	-5.16	-4.64
SF-539	-5.68	-4.99	-4.54
SNB-19	-5.57	-5.07	-4.51
SNB-75	-5.62	-5.19	-4.38
SNB-78	-5.70	-5.12	-4.59
U251	-5.65	-5.44	-5.08
XF 498	-5.77		
Melanoma		-5.27	> -4.12
LOX IMVI	-5.73	-5.54	-5.26
MALME-3M	-5.82	-5.61	-5.33
M14	-5.90	-5.40	> -4.12
M19 MEL	-5.88	-5.50	-5.18
SK-MEL-2	-5.82	-5.46	-4.94
SK-MEL-28	-5.86	-5.55	-5.27
SK-MEL-5	-5.84	-5.49	-5.16
UACC-257	-5.83	-5.38	-4.67
UACC-62	-5.78		
Ovarian Cancer		-5.46	-4.41
IGROV1	-5.85	-5.14	-4.61
OVCAR-3	-6.16	-5.62	-5.34
OVCAR-4	-5.90	-5.52	-5.24
OVCAR-5	-5.80	-5.28	> -4.12
OVCAR-8	-5.82	-4.82	-4.46
SK-OV-3	-5.30		
Renal Cancer		-5.52	-5.21
786-0	-5.84	-5.56	-5.24
ACHN	-5.88	-5.35	-4.87
CAKI-1	-5.68	-5.64	-5.36
RXF 393	-5.93	-5.10	-4.36
RXF 631	-5.68	-5.35	-4.75
SN12C	-5.75	-5.31	-4.72
TK-10	-5.74	-5.54	-5.20
UO-31	-5.88		
MG_MID	-5.83	-5.35	-4.68
Delta	0.84	0.76	0.68
Range	1.37	1.33	1.23

+3 +2 +1 0 -1 -2 -3

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TABLE 7 **Mean Graphs** BCH-674

NSC: 636529-N/ 1 | Units: Molar | SSPL: | Exp. ID: 90110SC22

Report Date: N. ember 2., 1990 | Test Date: October 22, 1990

Panel/Cell Line	Log_{10} GI50	GI50	Log_{10} TGI	TGI	Log_{10} LC50	LC50
Leukemia						
CCRF-CEM	-4.97		-4.44		> -4.00	
HL-60(TB)						
K-562	-4.89		-4.34		> -4.00	
MOLT-4	-5.18		-4.55		> -4.00	
RPMI-8226	-5.21		-4.57		-4.00	
SR-WJU						
Non-Small Cell Lung Cancer						
A549/ATCC	-4.84		-4.49		-4.15	
EKVX	-4.74		-4.42		-4.10	
HOP-18	-4.77		-4.50		-4.22	
HOP-62						
HOP-92	-5.55		-4.80		-4.29	
NCI-H226	-4.85		-4.51		-4.17	
NCI-H23	-4.76		-4.38		> -4.00	
NCI-H460	-4.81		-4.48		-4.15	
NCI-H522	> -5.00		> -5.00		> -5.00	
LXFL-529L	-4.93		-4.59		-4.24	
Small Cell Lung Cancer						
DMS 114	-5.02		-4.40		> -4.00	
DMS 273	-4.74		-4.40		-4.05	
Colon Cancer						
COLO 205	-4.64		-4.18		> -4.00	
HCC-2998	-4.89		-4.54		-4.20	
HCT-116	-4.80		-4.42		-4.03	
HCT-15	-4.85		-4.39		> -4.00	
HT29	-5.59		-5.12		-4.43	
KM12	-4.60		-4.08		> -4.00	
KM20L2	-4.77		-4.44		-4.12	
SW-620	-4.78		-4.47		-4.16	
CNS Cancer						
SF-268	-4.89		-4.50		-4.11	
SF-295	-4.80		-4.47		-4.15	
SF-539	-4.75		-4.49		-4.23	
SNB-19	> -5.00		> -5.00		> -5.00	
SNB-75	-4.98		-4.63		-4.28	
SNB-78	-4.85		-4.50		-4.15	
U251	-4.92		-4.61		-4.29	
XF-498	-4.82		-4.52		-4.22	
Melanoma						
LOX IMVI	-5.03		-4.54		-4.07	
MALME-3M	-4.76		-4.47		-4.19	
M14	-4.84		-4.47		-4.09	
MDA-MB-435	-4.76		-4.31		> -4.00	
SK-MEL-2	-4.84		-4.50		-4.17	
SK-MEL-28	-4.82		-4.47		-4.12	
SK-MEL-5	-4.85		-4.51		-4.17	
UACC-257	-5.10		-4.58		-4.12	
UACC-62	-4.69		-4.19		> -4.00	
Ovarian Cancer						
IGROV1	-4.76		-4.29		> -4.00	
OVCAR-3	-4.73		-4.37		-4.02	
OVCAR-4	-4.99		-4.64		-4.30	
OVCAR-5	-4.80		-4.53		-4.25	
OVCAR-8	-4.78		-4.39		-4.00	
SK-OV-3	-4.71		-4.41		-4.10	
Renal Cancer						
786-0	-4.82		-4.55		-4.27	
ACHN	-4.86		-4.57		-4.29	
CAKI-1	-5.27		-4.72		-4.29	
RXF-393	-5.43		-4.76		-4.33	
SN12C	-4.86		-4.41		> -4.00	
TK-10	-4.81		-4.49		-4.18	
UO-31	-4.87		-4.57		-4.27	
	-5.45		-4.81		-4.35	
MG_MID	-4.91		-4.52		-4.17	
Delta	0.68		0.61		0.26	
Range	0.99		1.04		0.43	

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TABLE 8 **Mean Graphs** BCH-675

NSC: 636530-0/ 1 | Units: Molar | SSPL: | Exp. ID: 90105C22

Report Date: November 26, 1990 | Test Date: October 22, 1990

Panel/Cell Line	Log_{10} GI50	GI50	Log_{10} TGI	TGI	Log_{10} LC50	LC50
Leukemia						
CCRF-CEM	-5.45		-4.82		> -4.00	
HL-60(TB)						
K-562	-5.41		-4.62		> -4.00	
MOLT-4	-5.56		-5.08		-4.10	
RPMI-8226	-5.69		-5.26		> -5.00	
SR-WJU						
Non-Small Cell Lung Cancer						
A549/ATCC	-4.81		-4.48		-4.15	
EKVX	-4.79		-4.46		-4.13	
HOP-18	-4.79		-4.53		-4.26	
HOP-62						
HOP-92	-5.52		-5.11		> -5.00	
NCI-H226	-4.73		-4.43		-4.13	
NCI-H23	-4.78		-4.39		> -4.00	
NCI-H322M	-4.89		-4.59		-4.30	
NCI-H460	-4.99		-4.62		-4.25	
NCI-H522	-5.67		-5.32		-4.79	
LXFL-529L	-5.34		-4.78		-4.37	
Small Cell Lung Cancer						
DMS 114	-5.35		-4.73		-4.17	
DMS 273	-4.93		-4.58		-4.24	
Colon Cancer						
COLO 205	-4.95		-4.51		-4.07	
HCC-2998	-5.21		-4.63		-4.10	
HCT-116	-5.59		-5.18		-4.44	
HCT-15	-5.20		-4.58		-4.02	
HT29	-4.82		-4.37		> -4.00	
KM12	-4.92		-4.29		> -4.00	
SW620	-4.88		-4.55		-4.21	
SW-620	-4.94		-4.54		-4.14	
CNS Cancer						
SF-268	-4.99		-4.52		-4.05	
SF-295	-4.84		-4.52		-4.20	
SF-539	-4.85		-4.57		-4.28	
SNB-19	> -5.00		> -5.00		> -5.00	
SNB-75	-5.42		-4.83		-4.38	
SNB-78	-4.91		-4.49		-4.06	
U251	-4.87		-4.58		-4.29	
SF-498	-4.93		-4.59		-4.24	
Melanoma						
LOXIMVI	-5.41		-4.76		> -4.00	
MALME-3M	-5.15		-4.68		-4.28	
M14	-5.00		-4.64		-4.28	
MDA-MB-435	-5.48		-4.86		-4.06	
SK-MEL-2	-5.32		-4.76		-4.24	
SK-MEL-28	-5.16		-4.67		-4.27	
SK-MEL-5						
UACC-257	-4.81		-4.47		-4.14	
UACC-62	-5.54		-4.93		> -4.00	
Ovarian Cancer						
IGROV1	-5.10		-4.54		-4.04	
OVCAR-3	-5.49		-4.82		-4.32	
OVCAR-4	-5.40		-4.84		-4.40	
OVCAR-5	-4.78		-4.52		-4.26	
OVCAR-8	-4.85		-4.40		> -4.00	
SK-OV-3	-4.82		-4.51		-4.20	
Renal Cancer						
786-0	-4.84		-4.52		-4.21	
A498	-4.91		-4.61		-4.30	
ACHN	-4.84		-4.55		-4.27	
RXF-393	-5.65		-5.04		-4.42	
SN12C	-4.98		-4.53		-4.08	
TK-10	-4.89		-4.53		-4.17	
UO-31	-4.78		-4.49		-4.21	
	-5.42		-4.76		-4.37	
PC-3/MID	-5.10		-4.67		-4.24	
Mean	0.58		0.65		0.55	
Range	0.96		1.03		0.79	

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TABLE 9 **Mean Graphs** BCH-681

NSC: D- 638334 -Y/1	Units: Molar	SSPL: Y71X	Exp. ID: 9012NS84
Report Date: March 1, 1991		Test Date: December 18, 1990	

Panel/Cell Line	Log_{10} GI50	Log_{10} TGI	Log_{10} LC50
Leukemia			
CCRF-CEM	-5.66	-5.13	> -4.00
HL-60(TB)	-5.77	-5.39	-4.95
K-562	-5.63	-5.26	> -4.00
MOLT-4	-5.69	-5.13	> -4.00
RPMI-8226	-5.70	-5.15	> -4.00
SR			
Non-Small Cell Lung Cancer			
A549/ATCC	-5.74	-5.46	
EKVX	-5.48	-4.92	-4.46
HOP-62	-4.88	-4.58	-4.28
HOP-92	-5.61	-5.21	-4.65
NCI-H226	-5.32	-4.80	-4.32
NCI-H23			
NCI-H322M	-5.70	-5.34	-4.94
NCI-H460	-5.54	-4.87	-4.06
NCI-H522	-5.79	-5.48	-5.18
LXFL-529L	-5.78	-5.52	-5.26
Small Cell Lung Cancer			
DMS 114	-5.73	-5.45	-5.18
DMS 273	-5.81	-5.49	-5.18
Colon Cancer			
COLO 205	-4.32	-5.75	-5.37
DLD-1	-5.80	-5.51	-5.23
HCC-2998			
HCT-116	-5.82	-5.47	-5.11
HCT-15	-5.85	-5.56	-5.26
HT29	-5.89	-5.57	-5.26
KM12	-5.53	-5.02	-4.46
KM20L2	-5.76	-5.47	-5.18
SW-620	-5.84	-5.56	-5.28
CNS Cancer			
SF-268	-5.51	-4.96	-4.45
SF-295	-5.52	-4.93	-4.46
SF-539	-5.73	-5.37	-5.02
SNB-19	-5.25	-4.74	-4.37
SNB-75	-5.60	-5.29	-4.94
SNB-78	-5.44	-4.75	> -4.00
U251	-5.53	-5.07	-4.54
XF 498	-5.74	-5.29	-4.74
Melanoma			
LOX IMVI	-5.87	-5.57	-5.27
MALME-3M	-5.65	-5.43	-5.21
M14	-5.84	-5.56	-5.28
M19-MEL	-4.60	-4.13	-5.58
SK-MEL-28	-5.74	-5.45	-5.16
SK-MEL-5	-5.84	-5.56	-5.28
UACC-257	-5.80	-5.52	-5.25
UACC-62	-6.22	-5.72	-5.34
Ovarian Cancer			
IGROV1	-5.67	-5.35	-5.02
OVCAR-3	-5.72	-5.31	-4.78
OVCAR-4	-5.59	-5.26	-4.81
OVCAR-5	-5.40	-5.17	-4.81
OVCAR-8	-5.49	-4.95	-4.47
Renal Cancer			
786-0	-5.53	-4.95	-4.47
A498	-4.89	-4.56	-4.23
ACHN	-5.76	-5.49	-5.23
CAKI-1	-5.29	-4.69	-4.12
RXF-393	-5.75	-5.36	-4.89
RXF-631	-5.65	-5.04	> -4.00
SN12C	-5.81	-5.53	-5.26
TK-10	-5.44	-5.03	-4.50
UO-31	-5.57	-5.11	-4.57
MG_MID	-5.67	-5.26	-4.79
Delta	0.94	0.87	0.80
Range	1.73	1.58	1.58

+3 +2 +1 0 -1 -2 -3

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TABLE 10 Mean Graphs BCH-683

Report Date: March , 1991

Test Date: December 18, 1990

Panel/Cell Line	Log_{10} GI50	GI50	Log_{10} TGI	TGI	Log_{10} LC50	LC50
Leukemia						
CCRF-CEM	-5.71		-5.26		> -4.00	
HL-60(TB)	-5.74		-5.33		> -4.00	
K-562	-5.79		-5.29		> -4.00	
MOLT-4	-5.79		-5.43		-5.06	
RPMI-8226	-5.74		-5.28		-4.04	
SR						
Non-Small Cell Lung Cancer						
A549/ATCC	-5.73		-5.45			
EKVX	-5.39		-4.85		-4.41	
HOP-62	-5.10		-4.67		-4.29	
HOP-92	-5.67		-5.35		-5.03	
NCI-H226	-5.23		-4.69		-4.24	
NCI-H23	-5.50		-4.90		-4.01	
NCI-H322M	-5.57		-5.12		-4.48	
NCI-H460	-5.38		-4.70		-4.18	
NCI-H522	-5.83		-5.50		-5.16	
LXFL-529L	-5.74		-5.46		-5.18	
Small Cell Lung Cancer						
DMS 114	-5.73		-5.40			
DMS 273	-5.73		-5.40		-5.08	
Colon Cancer						
COLO 205	-6.42		-5.89		-5.37	
DLD-1	-5.80		-5.52		-5.24	
HCC-2998						
HCT-116	-5.77		-5.43		-5.09	
HCT-15	-5.91		-5.57		-5.23	
HT29	-5.93		-5.42		> -4.00	
KM12	-5.55		-5.01		-4.26	
KM20L2	-5.74		-5.26		-4.55	
SW-620	-5.95		-5.55		-5.15	
CNS Cancer						
SF-268	-5.54		-4.94		-4.38	
SF-295	-5.55		-4.81		-4.36	
SF-539	-5.66		-5.24		-4.67	
SNB-19	-5.13		-4.70		-4.35	
SNB-75	-5.35		-4.82		-4.39	
SNB-78	-5.58		-4.93		> -4.00	
U251	-5.60		-5.07		-4.41	
XF 498	-5.55		-5.27		-4.95	
Melanoma						
LOX IMVI	-5.96		-5.63		-5.29	
MALME-3M	-5.82		-5.53			
M14	-5.77		-5.49		-5.21	
MDA-MB-435	-6.47		-6.03		-5.24	
SK-MEL-28	-5.63		-5.23		-4.62	
SK-MEL-5	-5.97		-5.65		-5.32	
UACC-257	-5.84		-5.49		-5.13	
UACC-62	-6.16		-5.66		-5.24	
Ovarian Cancer						
IGROV1	-5.67		-5.30		-4.67	
OVCAR-3	-5.84		-5.29		-4.67	
OVCAR-4	-5.77		-5.51		-5.25	
OVCAR-5	-5.49		-5.29		-5.10	
OVCAR-8	-5.63		-5.00		-4.34	
Renal Cancer						
786-0	-5.51		-4.93		-4.44	
A498	-4.85		-4.55		-4.25	
ACHN	-5.38		-4.86		-4.35	
CAKI-1	-5.38		-4.81		-4.22	
RXF-393	-5.86		-5.47		-5.07	
RXF-631	-5.72		-5.19		> -4.00	
SN12C	-5.84		-5.54		-5.24	
TK-10	-5.36		-4.84		-4.41	
UO-31	-5.62		-5.22		-4.69	
MG_MID	-5.67		-5.24		-4.66	
Delta	0.80		0.79		0.71	
Range	1.62		1.48		1.37	

National Cancer Institute Developmental Therapeutics Program

TABLE 11 **Mean Graphs** BCH-689

Report Date: Ma 1, 19[illegible] Test Date: December 18, 1990

Panel/Cell Line	Log_{10} GI50	GI50	Log_{10} TGI	TGI	Log_{10} LC50	LC50
Leukemia						
CCRF-CEM	-4.77		-4.24		> -4.18	
HL-60(TB)	-4.84		-4.49		> -4.18	
K-562	-4.80		-4.30		> -4.18	
MOLT-4	-4.78		> -4.18		> -4.18	
RPMI-8226	-4.86		-4.24		> -4.18	
SR						
Non-Small Cell Lung Cancer						
A549/ATCC	-4.82		-4.45		> -4.18	
EKVX	-4.73		-4.21		> -4.18	
HOP-62	-4.99		-4.68		-4.38	
HOP-92	-4.81		-4.60		-4.39	
NCI-H226	-4.93		-4.65		-4.37	
NCI-H23						
NCI-H322M	-4.63		> -4.18		> -4.18	
NCI-H460	-4.91		-4.58		-4.26	
NCI-H522	-5.03		-4.74		-4.45	
LXFL-529L	-4.98		-4.71		-4.44	
Small Cell Lung Cancer						
DMS 114	-4.92		-4.62		-4.32	
DMS 273	-4.96		-4.69		-4.42	
Colon Cancer						
COLO 205	-5.03		-4.74		-4.46	
DLD-1	-4.95		-4.66		-4.38	
HCC-2998						
HCT-116	-4.94		-4.67		-4.40	
HCT-15	-5.00		-4.72		-4.44	
HT29	-4.87		-4.62		-4.36	
KM12	-4.89		-4.65		-4.41	
KM20L2						
SW-620	-4.96		-4.69		-4.42	
CNS Cancer						
SF-268						
SF-295	-4.94		-4.66		-4.37	
SF-539	-5.02		-4.74		-4.45	
SNB-19	-4.74		> -4.18		> -4.18	
SNB-75	-4.87		-4.59		-4.31	
SNB-78	-4.73		-4.31		> -4.18	
U251	-4.95		-4.67		-4.39	
XF 498	-4.96		-4.69		-4.43	
Melanoma						
LOX IMVI	-4.93		-4.65		-4.35	
MALME-3M	-4.82		-4.58		-4.34	
M14	-4.94		-4.68		-4.42	
M19-MEL	-4.87		-4.62		-4.38	
SK-MEL-28	-4.84		-4.59		-4.34	
SK-MEL-5	-4.98		-4.72		-4.45	
UACC-257	-4.90		-4.64		-4.38	
UACC-62	-4.88		-4.63		-4.38	
Ovarian Cancer						
IGROV1	-4.85		-4.56		-4.27	
OVCAR-3	-4.95		-4.64		-4.33	
OVCAR-4	-4.94		-4.67		-4.41	
OVCAR-5						
OVCAR-8	-5.00		-4.73		-4.45	
Renal Cancer						
786-0	-4.95		-4.69		-4.44	
A498	-4.97		-4.57		> -4.18	
ACHN	-4.97		-4.71		-4.44	
CAKI-1	-4.97		-4.71		-4.44	
RXF-393	-4.98		-4.71		-4.43	
RXF-631	-4.88		-4.39		> -4.18	
SN12C	-4.97		-4.70		-4.43	
TK-10	-4.89		-4.65		-4.41	
UO-31	-5.01		-4.73		-4.45	
MG_MID	-4.90		-4.58		-4.34	
Delta	0.13		0.16		0.12	
Range	0.40		0.56		0.28	

+3 +2 +1 0 -1 -2 -3

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TABLE 12 **Mean Graphs** D-H-612 | **Report Date:** December 6, 1990 | **Test Date:** October 22, 1990

Panel/Cell Line	Log_{10} GI50	GI	Log_{10} TGI	TGI	Log_{10} LC50	LC50
Leukemia						
CCRF-CEM	-5.93		-5.45		> -4.31	
HL-60(TB)					> -4.31	
K-562	-5.73		-5.11		-4.61	
MOLT-4	-5.95		-5.53		-4.36	
RPMI 8226	-5.94		-5.22			
SR-WIU						
Non-Small Cell Lung Cancer						
A549/ATCC	-5.26		-4.88		-4.49	
EKVX	-5.60		-5.07		-4.65	
HOP-18	-5.13		-4.85		-4.58	
HOP-62						
HOP-92						
NCI-H226	-5.09		-4.75		-4.42	
NCI-H23	-5.44		-4.92		-4.47	
NCI-H460	-5.55		-5.01		-4.58	
NCI-H522	-6.04		-5.61		-4.60	
LXFL-529L	-5.52		-5.03		-4.66	
Small Cell Lung Cancer						
DMS 114	-5.83		-5.19		> -4.31	
DMS 273	-5.55		-5.02		-4.60	
Colon Cancer						
COLO 205	-5.84		-5.22		> -4.31	
DLD-1	-5.83		-5.23		-4.74	
HCC-2998						
HCT-116	-5.86		-5.31		-4.74	
HCT-15	-5.86		-5.25		-4.38	
HT29	-5.86		-5.30		-4.44	
KM12	-5.31		-4.96		-4.61	
KM20L2	-5.82		-5.27		-4.72	
SW-620	-5.82		-5.31		-4.57	
CNS Cancer						
SF-268	-5.77		-5.09		> -4.31	
SF-295	-5.16		-4.82		-4.49	
SF-539	-5.22		-4.91		-4.61	
SNB-19	-5.20		-4.89		-4.59	
SNB-75	-5.06		-4.79		-4.52	
SNB-78	-5.60		-4.99		-4.44	
U251	-5.11		-4.84		-4.57	
XF 498	-5.55		-5.05		-4.67	
Melanoma						
LOX IMVI	-5.73		-5.06		-4.31	
MALME-3M	-5.96		-5.48		-4.86	
M14	-5.85		-5.29		-4.75	
M19 MEL	-5.95		-5.54		-4.90	
SK-MEL-2	-5.63		-5.02		-4.64	
SK-MEL-28	-5.53		-5.02		-4.61	
SK-MEL-5	-5.87		-5.38		-4.75	
UACC-257	-5.91		-5.36		-4.71	
UACC-62	-5.86		-5.24		-4.47	
Ovarian Cancer						
IGROV1	-5.74		-5.08		-4.37	
OVCAR-3	-5.78		-5.26		-4.78	
OVCAR-4	-5.44		-5.01		-4.65	
OVCAR-5	-5.05		-4.80		-4.56	
OVCAR-8	-5.94		-5.46		-4.64	
SK-OV-3	-5.05		-4.79		-4.53	
Renal Cancer						
786-0	-5.39		-4.98		-4.62	
ACHN	-5.39		-4.99		-4.64	
CAKI-1	-5.12		-4.84		-4.55	
RXF-393	-5.69		-5.11		-4.70	
RXF-631	-5.39		-4.95		-4.56	
SN12C	-5.86		-5.31		-4.77	
TK-10	-5.02		-4.77		-4.52	
UO-31	-5.20		-4.91		-4.61	
MG_MID	-5.58		-5.10		-4.57	
Delta	0.45		0.51		0.33	
Range	1.02		0.86		0.59	

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Example 17

In Vitro Clonogenic Assays of Heteroanthracyclinones.

Tables 13 and 14 summarize the GI_{50} and LC_{50} average values obtained from a group of cell lines, per type of cancer, for various heteroanthracyclinones. The original results obtained from the NCI, Bethesda, Maryland, for these compounds are shown in tables 15 to 22. The same protocol as used for BCH-242 in example 15 was employed in this example.

It is most interesting to note that some of the heteroanthrocyclinones (BCH-651, BCH-657, BCH-660) listed in tables 13 and 14 show strong antiproliferative (GI_{50}) and potent cytotoxic (LC_{50}) activities. In the case of BCH-657 and BCH-660 the mean LC_{50} potency in solid tumors is similar to the one observed for DNM and ADR. The same trend observed with the heteroanthracyclines of example 16, where antileukemic activity is depressed, recurs with the heteroanthracyclinones of this example. This aspect may be beneficial to the clinical use of heteroanthracyclinones in the chemotherapy of solid tumors.

BCH-687, a compound in which there are no benzylic substituents, has significant antiproliferative (GI_{50}) and cytotoxic (LC_{50}) activities in solid tumors. This is unprecedented because known anthracyclinones which lack benzylic substituents are normally devoid of anticancer activity.

TABLE 13

Average LOG$_{10}$ GI$_{50}$ Multiple cell lines

BCH no.	Leukemia	NSC lung	SC lung	Colon	CNS	Melanoma	Ovarian	Renal	Mean Potency in solid tumors
DNM	-7.25±0.10	-7.04±0.23	-7.14±0.01	-6.82±0.31	-7.04±0.15	-6.95±0.21	-6.86±0.18	-6.79±0.47	-6.95±0.22
ADR	-7.51±0.52	-7.33±0.76	-7.27±0.12	-6.61±0.35	-7.07±0.26	-6.92±0.26	-6.55±0.19	-6.74±0.41	-6.93±0.29
650	-4.21±0.16(3R)	>-4.00	>-4.00	>-4.00	-4.34±0.15(1R)*	>-4.00	>-4.00	-4.28±0.20(4R)	-4.28±0.05
651	-5.48±0.06	-5.11±0.33	-5.56±0.09	-5.47±0.12	-5.00±0.25	-5.56±0.13	-5.23±0.12	-5.00±0.27	-5.28±0.23
653	4.80±0.40	-4.35±0.20(3R)	-4.54±0.06	-4.45±0.12(1R)	-4.30±0.17(1R)	-4.48±0.16	-4.42±0.23	-4.24±0.22(3R)	-4.40±0.10
657	-6.36±0.06	-5.95±0.36	-5.90±0.26	-6.10±0.30	-5.73±0.14	-5.87±0.22	-5.77±0.22	-5.88±0.25	-5.89±0.11
658	>-4.00	>-4.00	>-4.00	-4.21±0.10(4R)	-4.33±0.16	>-4.00	>-4.00	-4.33±0.17(4R)	-4.29±0.06
660	-6.50±0.08	-6.01±0.55(1R)	-6.00±0.28	-6.21±0.25	-6.02±0.24	-6.02±0.28	-6.02±0.24	-6.04±0.34	-6.05±0.07
687	-4.91±0.12	4.81±0.35	-5.09±0.25	-4.95±0.28	-4.59±0.16	-5.05±0.27	-4.94±0.37	-4.69±0.23	-4.87±0.17
688	-4.44±0.21	>-4.00	>-4.00	>-4.00	-4.27±0.14(3R)	>-4.00	-4.12±0.01(2R)	>-4.00	-4.28±0.13

* Represents the number of cell lines which are considered to be refractory towards the compound's cytotoxicity (LOG$_{10}$ GI$_{50}$ <-4.00).

TABLE 14

Average LOG $LC_{10\ 50}$ Multiple cell lines

BCH no.	Leukemia	NSC lung	SC lung	Colon	CNS	Melanoma	Ovarian	Renal	Mean Potency in solid tumors
DNM	-4.30±0.36	-5.07±0.37	-5.58±0.09	-4.83±0.37	-5.08±0.42	-5.64±0.17	-4.78±0.20	-4.78±0.46	-5.11±0.34
ADR	-4.76±0.10	-5.01±0.26	-5.39±0.18	-4.86±0.27	-5.03±0.35	-5.56±0.29	-4.74±0.05	-4.87±0.38	-5.07±0.28
650	>-4.00	>-4.00	>-4.00	>-4.00	>-4.00	>-4.00	>-4.00	>-4.00	>>-4.00
651	>-4.00	-4.30±0.36(3R)*	-4.21±0.01	-4.38±0.11(2R)	-4.19±0.10	-4.46±0.23	-4.33±0.04(1R)	-4.26±0.10	-4.30±0.09
653	>-4.00	>-4.00	>-4.00	>-4.00	>-4.00	>-4.00	>-4.00	>-4.00	>-4.00
657	>-4.00	-4.94±0.31(4R)	>-4.00	-4.87±0.43(6R)	-4.88±0.36(2R)	-4.88±0.29(4R)	-4.76±0.39(1R)	-4.92±0.49	-4.88±0.06
658	>-4.00	>-4.00	>-4.00	>-4.00	>-4.00	>-4.00	>-4.00	>-4.00	>4.00
660	>-4.00	-4.71±0.43(2R)	>-4.00	>-4.00	-4.80±0.45	-4.98±0.42(3R)	-5.18±0.08(1R)	-5.10±0.40	-4.95±0.18
687	>-4.00	>-4.23(±0.07)	>-4.18	-4.25(±0.09)3R	>-4.15	-4.28(±0.09)1R	-4.15(±0.11)2R	>-4.21	-4.21(±0.05)
688 *	>-4.00	>-4.00	>-4.00	>-4.00	>-4.00	>-4.00	>4.00	>-4.00	>-4.00

* Represents the number of cell lines which are considered to be refractory towards the compound's cytotoxicity (LOG $LC_{10\ 50}$ <-4.00).

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NSC: D-638327-R/1 | Units: Molar | SSPL: [illegible] | Exp. ID: [illegible]

TABLE 15 **Mean Graphs** BCH-650

Report Date: Mar. 1, 1991 | **Test Date:** December 18, 1990

Panel/Cell Line	Log_{10} GI50	GI50	Log_{10} TGI	TGI	Log_{10} LC50	LC50
Leukemia						
CCRF-CEM	> -4.00		> -4.00		> -4.00	
HL-60(TB)	-4.13		> -4.00		> -4.00	
K-562	> -4.00		> -4.00		> -4.00	
MOLT-4	-4.07		> -4.00		> -4.00	
RPMI-8226	-4.44		> -4.00		> -4.00	
SR	> -4.00		> -4.00		> -4.00	
Non-Small Cell Lung Cancer						
A549/ATCC	> -4.00		> -4.00		> -4.00	
EKVX	> -4.00		> -4.00		> -4.00	
HOP-62	-4.35		> -4.00		> -4.00	
HOP-92	-4.28		> -4.00		> -4.00	
NCI-H226	> -4.00					
NCI-H23			> -4.00		> -4.00	
NCI-H322M	> -4.00		> -4.00		> -4.00	
NCI-H460	> -4.00		> -4.00		> -4.00	
NCI-H522	-4.04		> -4.00		> -4.00	
LXFL-529L	> -4.00					
Small Cell Lung Cancer			> -4.00		> -4.00	
DMS 114	> -4.00		> -4.00		> -4.00	
DMS 273	> -4.00					
Colon Cancer			> -4.00		> -4.00	
COLO 205	> -4.00		> -4.00		> -4.00	
DLD-1	> -4.00					
HCC-2998			> -4.00		> -4.00	
HCT-116	> -4.00		> -4.00		> -4.00	
HCT-15	> -4.00		> -4.00		> -4.00	
HT29	> -4.00		> -4.00		> -4.00	
KM12	> -4.00					
KM20L2			> -4.00		> -4.00	
SW-620	> -4.00					
CNS Cancer						
SF-268			> -4.00		> -4.00	
SF-295	> -4.00		> -4.00		> -4.00	
SF-539	-4.01		> -4.00		> -4.00	
SNB-19	-4.31		-4.07		> -4.00	
SNB-75	-4.48		> -4.00		> -4.00	
SNB-78	-4.39		> -4.00		> -4.00	
U251	-4.47		> -4.00		> -4.00	
XF 498	-4.36					
Melanoma			> -4.00		> -4.00	
LOX IMVI	-4.06		> -4.00		> -4.00	
MALME-3M	> -4.00		> -4.00		> -4.00	
M14	> -4.00		> -4.00		> -4.00	
M19-MEL	> -4.00		> -4.00		> -4.00	
SK-MEL-28	> -4.00		> -4.00		> -4.00	
SK-MEL-5	> -4.00		> -4.00		> -4.00	
UACC-257	> -4.00		> -4.00		> -4.00	
UACC-62	> -4.00					
Ovarian Cancer			> -4.00		> -4.00	
IGROV1	> -4.00		> -4.00		> -4.00	
OVCAR-3	> -4.00		> -4.00		> -4.00	
OVCAR-4	-4.52		> -4.00		> -4.00	
OVCAR-5	> -4.00		> -4.00		> -4.00	
OVCAR-8	> -4.00					
Renal Cancer			> -4.00		> -4.00	
786-0	-4.03		> -4.00		> -4.00	
A498	> -4.00		> -4.00		> -4.00	
ACHN	-4.29		> -4.00		> -4.00	
CAKI-1	> -4.00		-4.07		> -4.00	
RXF-393	-4.55		> -4.00		> -4.00	
RXF-631	-4.09		> -4.00		> -4.00	
SN12C	> -4.00		> -4.00		> -4.00	
TK-10	-4.46		> -4.00		> -4.00	
UO-31	> -4.00					
MG_MID	-4.10		-4.00		-4.00	
Delta	0.45		0.07		0.00	
Range	0.55		0.07		0.00	

+3 +2 +1 0 -1 -2 -3

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TABLE 16 **Mean Graphs** BCH-651

NSC: D-638328-S/1 | Units: Molar | SSPL: 171A | Exp. ID: 901ZN584

Report Date: March 1, 19.. | Test Date: December 18, 1990

Panel/Cell Line	Log_{10} GI50	Log_{10} TGI	Log_{10} LC50
Leukemia			
CCRF-CEM	-5.41	> -4.00	> -4.00
HL-60(TB)	-5.49	> -4.00	> -4.00
K-562	-5.46	> -4.00	> -4.00
MOLT-4	-5.49	> -4.00	> -4.00
RPMI-8226	-5.60	> -4.00	> -4.00
SR	-5.45	> -4.00	> -4.00
Non-Small Cell Lung Cancer			
A549/ATCC	-5.11	-4.54	-4.02
EKVX	-5.32	-4.76	-4.33
HOP-62	-4.83	-4.40	> -4.00
HOP-92	-5.24	-4.64	> -4.00
NCI-H226	-4.73	-4.37	-4.01
NCI-H23			
NCI-H322M	-4.80	-4.33	> -4.00
NCI-H460	-4.80	-4.45	-4.09
NCI-H522	-5.73	-5.38	-5.04
LXFL-529L	-5.47	-4.88	-4.40
Small Cell Lung Cancer			
DMS 114	-5.45	-5.28	-4.20
DMS 273	-5.48	-4.86	-4.22
Colon Cancer			
COLO 205	-5.36	-4.80	-4.36
DLD-1	-5.47	-4.93	> -4.00
HCC-2998			
HCT-116	-5.73	-5.28	-4.55
HCT-15	-5.55	-4.95	-4.41
HT29	-5.39	-4.73	> -4.00
KM12	-5.43	-4.88	-4.37
KM20L2			
SW-620	-5.37	-4.84	-4.21
CNS Cancer			
SF-268			
SF-295	-4.84	-4.55	-4.25
SF-539	-5.02	-4.63	-4.26
SNB-19	-4.93	-4.51	-4.09
SNB-75	-4.74	-4.38	-4.02
SNB-78	-5.06	> -4.00	> -4.00
U251	-5.57	-5.15	-4.23
XF 498	-4.84	-4.56	-4.27
Melanoma			
LOX IMVI	-5.59	-4.92	-4.41
MALME-3M	-5.69	-5.20	-4.58
M14	-5.61	-5.14	-4.56
M19-MEL	-5.52	-5.05	-4.28
SK-MEL-28	-5.24	-4.60	-4.04
SK-MEL-5	-5.67	-5.31	-4.88
UACC-257	-5.60	-5.16	-4.53
UACC-62	-5.52	-5.07	-4.38
Ovarian Cancer			
IGROV1	-4.95	-4.39	> -4.00
OVCAR-3	-5.63	-5.24	-4.37
OVCAR-4	-5.28	-4.74	-4.35
OVCAR-5	-4.79	-4.53	-4.26
OVCAR-8	-5.51	-4.96	-4.33
Renal Cancer			
786-0	-5.08	-4.61	-4.18
A498	-4.73	-4.46	-4.20
ACHN	-5.13	-4.69	-4.31
CAKI-1	-4.84	-4.49	-4.13
RXF-393	-5.56	-5.04	-4.47
RXF-631	-4.91	-4.11	> -4.00
SN12C	-5.19	-4.69	-4.29
TK-10	-4.60	-4.40	-4.19
UO-31	-4.93	-4.61	-4.30
MG_MID	-5.26	-4.67	-4.23
Delta	0.47	0.71	0.80
Range	1.13	1.38	1.04

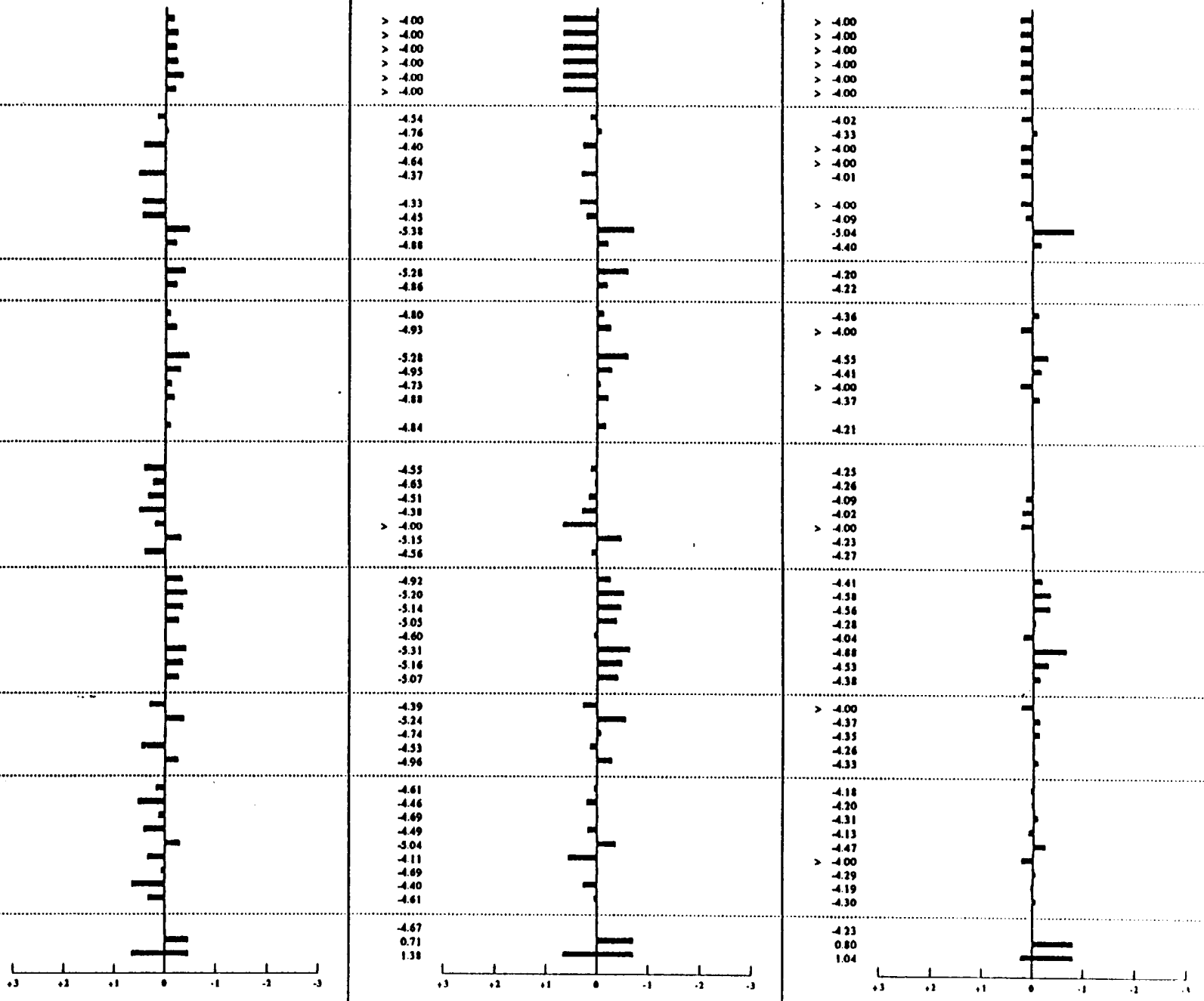

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TABLE 17 **Mean Graphs** BCH-6575

Report Date: M..ch 1, 1991 | Test Date: December 18, 1990

Panel/Cell Line	Log_{10} GI50	Log_{10} TGI	Log_{10} LC50
Leukemia			
CCRF-CEM	-4.93	-4.37	> -4.00
HL-60(TB)	-4.93	-4.40	> -4.00
K-562	-4.81	-4.36	> -4.00
MOLT-4	-4.68	-4.23	> -4.00
RPMI-8226	-4.77	-4.28	> -4.00
SR	-4.66	-4.20	> -4.00
Non-Small Cell Lung Cancer			
A549/ATCC	-4.06	> -4.00	> -4.00
EKVX	-4.27	> -4.00	> -4.00
HOP-62	> -4.00	> -4.00	> -4.00
HOP-92	-4.24	> -4.00	> -4.00
NCI-H226	> -4.00	> -4.00	> -4.00
NCI-H23			
NCI-H322M	-4.40	> -4.00	> -4.00
NCI-H460	> -4.00	> -4.00	> -4.00
NCI-H522	-4.73	-4.20	> -4.00
LXFL-529L	-4.39	> -4.00	> -4.00
Small Cell Lung Cancer			
DMS 114	-4.60	-4.23	> -4.00
DMS 273	-4.48	> -4.00	> -4.00
Colon Cancer			
COLO 205	-4.39	> -4.00	> -4.00
DLD-1	-4.58	-4.09	> -4.00
HCC-2998			
HCT-116	-4.57	> -4.00	> -4.00
HCT-15	-4.56	> -4.00	> -4.00
HT29	-4.27	> -4.00	> -4.00
KM20L2	> -4.00	> -4.00	> -4.00
SW-620	-4.55	> -4.00	> -4.00
CNS Cancer			
SF-268 -			
SF-295	-4.09	> -4.00	> -4.00
SF-539	-4.41	> -4.00	> -4.00
SNB-19	-4.28	> -4.00	> -4.00
SNB-75	-4.08	> -4.00	> -4.00
SNB-78	-4.45	> -4.00	> -4.00
U251	-4.51	> -4.00	> -4.00
XF 498	> -4.00	> -4.00	> -4.00
Melanoma			
LOX IMVI	-4.60	> -4.00	> -4.00
MALME-3M	-4.30	> -4.00	> -4.00
M14	-4.29	> -4.00	> -4.00
MDA-MEL	-4.52	> -4.00	> -4.00
SK-MEL-28	-4.33	> -4.00	> -4.00
SK-MEL-5	-4.39	> -4.00	> -4.00
UACC-257	-4.63	-4.21	> -4.00
UACC-62	-4.74	-4.29	> -4.00
Ovarian Cancer			
IGROV1	-4.04	> -4.00	> -4.00
OVCAR-3	-4.64	-4.23	> -4.00
OVCAR-4	-4.49	> -4.00	> -4.00
OVCAR-8	-4.31	> -4.00	> -4.00
Renal Cancer			
786-0	-4.03	> -4.00	> -4.00
A498	> -4.00	> -4.00	> -4.00
ACHN	-4.49	> -4.00	> -4.00
CAKI-1	> -4.00	> -4.00	> -4.00
RXF-393	-4.50	-4.03	> -4.00
RXF-631	-4.37	> -4.00	> -4.00
SN12C	> -4.00	> -4.00	> -4.00
TK-10	-4.01	> -4.00	> -4.00
UO-31	-4.03	> -4.00	> -4.00
MG_MID	-4.37	-4.06	-4.00
Delta	0.36	0.34	0.00
Range	0.93	0.40	0.00

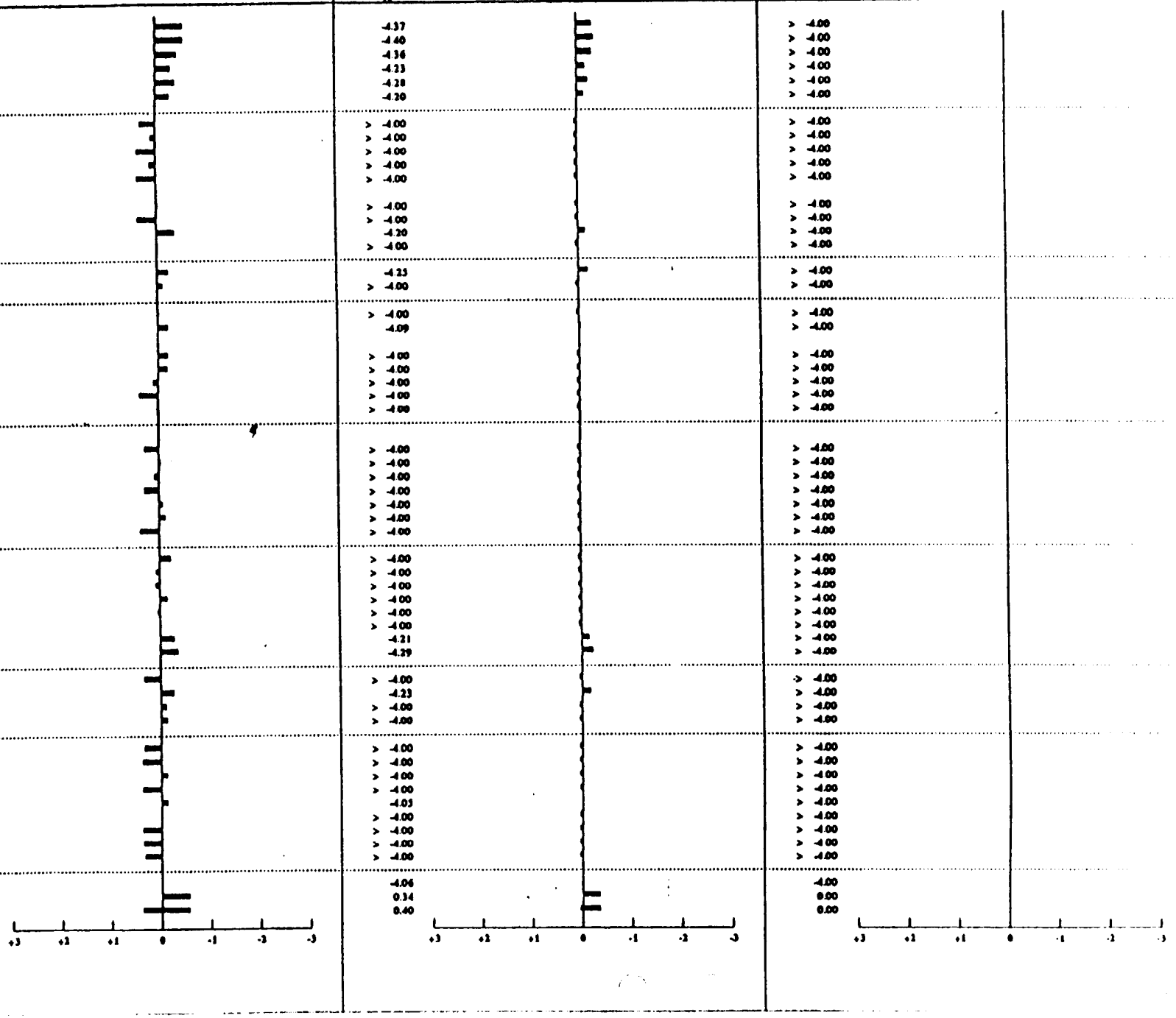

TABLE 18 **Mean Graphs** BCH-657 | **Report Date:** November 26, 1990 | **Test Date:** October 22, 1990

Panel/Cell Line	Log_{10} GI50	GI50	Log_{10} TGI	TGI	Log_{10} LC50	LC50
Leukemia						
CCRF-CEM	-6.38		-5.56		> -4.00	
HL-60(TB)						
K-562	-6.27		-5.40		> -4.00	
MOLT-4	-6.35		-5.53		-4.29	
RPMI-8226	-6.45		-5.67		> -4.00	
SR-WIU						
Non-Small Cell Lung Cancer						
A549/ATCC	-5.59		-5.09		-4.41	
EKVX	-5.62		-5.26		> -4.00	
HOP-18	-5.81		-5.50		-5.19	
HOP-62						
HOP-92	-6.55		> -6.00		> -6.00	
NCI-H226	-5.69		-5.32		-4.85	
NCI-H23	-5.89		-5.45		> -4.00	
NCI-H322M	-5.85		-5.41		-4.93	
NCI-H460	-5.68		-5.34		> -4.00	
NCI-H522	-6.62		-6.12			
LXFL-529L	-6.23		-5.71		-5.30	
Small Cell Lung Cancer						
DMS 114	-6.15		-5.49		> -4.00	
DMS 273	-5.64		-5.27		> -5.00	
Colon Cancer						
COLO 205	-6.10		-5.35		> -4.00	
DLD-1	-6.10		-5.44		-4.44	
HCC-2998						
HCT-116	-6.49		-5.92		-5.30	
HCT-15	-6.43		-5.48		> -4.00	
HT29	-5.79		-5.05		> -4.00	
KM12	-5.55		-4.78		> -4.00	
KM20L2	-6.32		-5.63		> -4.00	
SW-620	-6.02		-5.17		> -4.00	
CNS Cancer						
SF-268	-5.87		-5.39		> -5.00	
SF-295	-5.44		-4.98		-4.28	
SF-539	-5.78		-5.50		-5.22	
SNB-19	-5.83		-5.28		-4.54	
SNB-75	-5.82		-5.52		-5.22	
SNB-78	-5.61		-5.14		> -4.00	
U251	-5.86		-5.49		-5.13	
XF 498	-5.62		-5.29		-4.88	
Melanoma						
LOX IMVI	-5.79		-5.30		-4.37	
MALME-3M	-5.69		-5.35		-5.01	
M14	-5.92		-5.49		-5.05	
M19-MEL	-6.30		-5.53		> -4.00	
SK-MEL-2	-5.76		-5.42		-5.08	
SK-MEL-28	-6.12		-4.96		> -4.00	
SK-MEL-5						
UACC-257	-5.63		-5.19		> -4.00	
UACC-62	-5.73		-5.15		> -4.00	
Ovarian Cancer						
IOROV1	-5.92		-5.39		-4.29	
OVCAR-3	-5.85		-5.37		-4.72	
OVCAR-4	-5.79		-5.52		-5.25	
OVCAR-5	-5.74		-5.45		-5.15	
OVCAR-8	-6.01		-5.36		> -4.00	
SK-OV-3	-5.31		-4.77		-4.37	
Renal Cancer						
786-0	-5.75		-5.39		-5.03	
ACHN	-5.92		-5.60		-5.28	
CAKI-1	-5.50		-4.97		-4.29	
RXP-393	-6.41		-5.87		-5.43	
RXP-631	-5.84		-5.16		> -4.00	
SN12C	-5.92		-5.49		-5.06	
TK-10	-5.67		-5.34		-5.01	
UO-31	-6.00		-5.65		-5.31	
MG_MID	-5.93		-5.39		-4.58	
Delta	0.70		0.73		0.85	
Range	1.32		1.35		1.43	

+3 +2 +1 0 -1 -2 -3

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TABLE 19 **Mean Graphs** BCH-628

NSC: 636532-Q/ 1	Units: Molar	SSPL:	Exp. ID: 90H05C22
Report Date: November 26, 1990		Test Date: October 22, 1990	

Panel/Cell Line	Log_{10} GI50	GI50	Log_{10} TGI	TGI	Log_{10} LC50	LC50
Leukemia						
CCRF-CEM	> -4.00		> -4.00		> -4.00	
HL-60(TB)						
K-562	> -4.00		> -4.00		> -4.00	
MOLT-4	> -4.00		> -4.00		> -4.00	
RPMI-8226	> -4.00		> -4.00			
SR-WJU						
Non-Small Cell Lung Cancer						
A549/ATCC	> -4.00		> -4.00		> -4.00	
EKVX	> -4.00		> -4.00		> -4.00	
HOP-18	> -4.00		> -4.00		> -4.00	
HOP-62			-4.16		> -4.00	
HOP-92	-4.70		> -4.00		> -4.00	
NCI-H226	> -4.00		> -4.00		> -4.00	
NCI-H23	> -4.00		> -4.00		> -4.00	
NCI-H460	> -4.00		> -4.00		> -4.00	
NCI-H522	-4.52		> -4.00		> -4.00	
LXFL-529L	> -4.00					
Small Cell Lung Cancer						
DMS 114	-4.53		> -4.00		> -4.00	
DMS 273	> -4.00		> -4.00		> -4.00	
Colon Cancer						
COLO 205	> -4.00		> -4.00		> -4.00	
HCC-2998	> -4.00		> -4.00			
HCT-116			> -4.00		> -4.00	
HCT-15	-4.15		> -4.00		> -4.00	
HT29	-4.07		> -4.00		> -4.00	
KM12	-4.32		> -4.00		> -4.00	
KM20L2	> -4.00		> -4.00		> -4.00	
SW-620	-4.30		> -4.00		> -4.00	
CNS Cancer	> -4.00		> -4.00		> -4.00	
SF-268			> -4.00		> -4.00	
SF-295	-4.23		> -4.00		> -4.00	
SF-539	-4.33		> -4.00		> -4.00	
SNB-19	-4.41		> -4.00		> -4.00	
SNB-75	-4.31		-4.34		-4.00	
SNB-78	-4.68		> -4.00		> -4.00	
U251	-4.11		> -4.00		> -4.00	
XF 498	-4.32		> -4.00		> -4.00	
	-4.24		> -4.00		> -4.00	
Melanoma						
LOX IMVI	> -4.00		> -4.00		> -4.00	
MALME-3M	-4.28		> -4.00		> -4.00	
M14	> -4.00		> -4.00		> -4.00	
MDA-MB-435	-4.51		-4.00		> -4.00	
SK-MEL-2	-4.06		> -4.00		> -4.00	
SK-MEL-28	> -4.00		> -4.00		> -4.00	
SK-MEL-5						
UACC-257	> -4.00		> -4.00		> -4.00	
UACC-62	> -4.00		> -4.00		> -4.00	
Ovarian Cancer						
IGROV1	> -4.00		> -4.00		> -4.00	
OVCAR-3	-4.67		> -4.00		> -4.00	
OVCAR-4	> -4.00		> -4.00		> -4.00	
OVCAR-5	> -4.00		> -4.00		> -4.00	
OVCAR-8	-4.08		> -4.00		> -4.00	
SK-OV-3	> -4.00		> -4.00		> -4.00	
Renal Cancer						
786-0	-4.42		> -4.00		> -4.00	
A498	> -4.00		> -4.00		> -4.00	
ACHN	> -4.00		> -4.00		> -4.00	
CAKI-1	-4.54		-4.02		> -4.00	
RXF 393	-4.24		> -4.00		> -4.00	
RXF 631	> -4.00		> -4.00		> -4.00	
SN12C	-4.10		> -4.00		> -4.00	
TK-10	> -4.00		> -4.00		> -4.00	
UO-31						
Prostate Cancer	-4.15		-4.01		-4.00	
PC-3	0.54		0.33		0.00	
DU-145	0.70		0.34		0.00	
Breast Cancer						

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TABLE 20 **Mean Graphs** BCH-660

NSC: 636533-R/ 1	Units: Molar	SSPL:	Exp. ID: 9010SC22
Report Date: November 26, 1990		Test Date: October 22, 1990	

Panel Cell Line	Log_{10} GI50	GI50	Log_{10} TGI	TGI	Log_{10} LC50	LC50
Leukemia						
CCRF-CEM	-6.51		-5.91		> -4.00	
HL-60(TB)						
K-562	-6.40		-5.70		> -4.00	
MOLT-4	-6.47		-5.92		-5.10	
RPMI-8226	-6.63		-6.20		> -4.00	
SR-WIU						
Non-Small Cell Lung Cancer						
A549/ATCC	-5.69		-5.24		-4.55	
EKVX	-5.71		-5.34		-4.67	
HOP-18	-4.99		-4.61		-4.22	
HOP-62						
HOP-92	-6.58		-6.02		-5.39	
NCI-H226	> -6.00		> -6.00		> -6.00	
NCI-H23	-6.29		-5.67			
NCI-H460	-5.65		-5.25		> -4.00	
NCI-H522	-6.68		-6.23			
EKVX-529L	-6.48		-5.91		-5.43	
Small Cell Lung Cancer						
DMS 114	-6.27		-5.58		> -4.00	
DMS 273	-5.72		-5.37			
Colon Cancer						
COLO 205	-6.20		-5.37		> -4.00	
HCC-2998	-6.37		-5.65		> -4.00	
HCT-116	-6.49		-5.98		-5.46	
HCT-15	-6.47		-5.82		> -4.00	
HT29	-5.65		> -4.00		> -4.00	
KM12	-6.12		-5.40		> -4.00	
KM20L2	-6.13		-5.32		> -4.00	
SW-620	-6.27		-5.61		> -4.00	
CNS Cancer						
SF-268	-6.26		-5.38		-4.38	
SF-295	-5.65		-5.03		-4.09	
SF-539	-6.00		-5.67		-5.33	
SNB-19	-6.05		-5.30		-4.56	
SNB-75	-6.38		-5.83		-5.33	
SNB-78	-6.22		-5.51		> -4.00	
U251	-5.86		-5.37		-4.80	
XF 498	-5.76		-5.44		-5.13	
Melanoma						
LOX IMVI	-6.07		-5.49		> -4.00	
MALME-3M	-5.71		-5.39			
M14	-6.15		-5.66		-5.25	
MDA-MB-435	-6.42		-5.83			
SK-MEL-2	-5.67		-5.30		-4.39	
SK-MEL-28	-6.31		-5.75		-5.30	
SK-MEL-5						
UACC-257	-5.68		-5.27		> -4.00	
UACC-62	-6.19		-5.46		> -4.00	
Ovarian Cancer						
IGROV1	-6.07		-5.54		-5.04	
OVCAR-3	-6.26		-5.67		-5.18	
OVCAR-4	-5.92		-5.61		-5.29	
OVCAR-5	-5.76		-5.49		-5.22	
OVCAR-8	-6.36		-5.61		> -4.00	
SK-OV-3	-5.74		-5.45		-5.15	
Renal Cancer						
786-0	-5.98		-5.65		-5.31	
ACHN	-6.23		-5.61		-5.06	
CAKI-1	-5.47		-5.04		-4.25	
RXF-393	-6.55		-6.08		-5.55	
RXF-631	-5.92		-5.55		-5.18	
SN12C	-6.15		-5.69		-5.31	
TK-10	-5.66		-5.25		-4.70	
UO-31	-6.39		-5.86		-5.40	
Prostate						
PC-3/MD	-6.09		-5.55		-4.67	
DU-145	0.59		0.68		0.88	
Mean	1.69		2.23		1.55	

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TABLE 21 **Mean Graphs** BCH-687

Report Date: M...h 1, 1991 | Test Date: December 18, 1990

Panel/Cell Line	Log_{10} GI50	GI50	Log_{10} TGI	TGI	Log_{10} LC50	LC50
Leukemia						
CCRF-CEM	-4.74		> -4.00		> -4.00	
HL-60(TB)	-5.10		-4.17		> -4.00	
K-562	-4.87		-4.34		> -4.00	
MOLT-4	-4.89		-4.36		> -4.00	
RPMI-8226	-4.93		-4.44		> -4.00	
SR						
Non-Small Cell Lung Cancer						
A549/ATCC	-5.17		> -4.00		> -4.00	
EKVX	-4.78		-4.51		-4.24	
HOP-62	-4.52		-4.10		> -4.00	
HOP-92	-4.84		-4.49		-4.13	
NCI-H226	-4.19		> -4.00		> -4.00	
NCI-H23						
NCI-H322M	-4.66		> -4.00		> -4.00	
NCI-H460	-4.72		-4.04		> -4.00	
NCI-H522	-5.50		-4.78		> -4.00	
LXFL-529L	-4.93		-4.63		-4.31	
Small Cell Lung Cancer						
DMS 114	-5.33		-4.66		> -4.00	
DMS 273	-4.84		-4.51		-4.18	
Colon Cancer						
COLO 205	-5.25		-4.72		-4.32	
DLD-1	-4.89		-4.52		-4.14	
HCC-2998						
HCT-116	-5.12		-4.59		-4.13	
HCT-15	-5.23		-4.70		-4.30	
HT29	-4.66		-4.18		> -4.00	
KM12	-4.71		-4.30		> -4.00	
KM20L2	-4.51		-4.05		> -4.00	
SW-620	-5.21		-4.72		-4.34	
CNS Cancer						
SF-268	-4.52		> -4.00		> -4.00	
SF-295	-4.56		> -4.00		> -4.00	
SF-539	-4.91		-4.53		-4.15	
SNB-19	-4.55		> -4.00		> -4.00	
SNB-75	-4.47		-4.12		> -4.00	
SNB-78	-4.41		> -4.00		> -4.00	
U251	-4.74		-4.18		> -4.00	
XF 498						
Melanoma						
LOX IMVI	-4.94		-4.61		-4.27	
MALME-3M	-4.89		-4.59		-4.28	
M14	-4.84		-4.53		-4.21	
M19-MEL	-5.47		-5.00		-4.36	
SK-MEL-28	-4.72		-4.18		> -4.00	
SK-MEL-5	-5.36		-4.77		-4.37	
UACC-257	-5.32		-4.75		-4.33	
UACC-62	-4.87		-4.49		-4.11	
Ovarian Cancer						
IGROV1	-4.70		-4.35		> -4.00	
OVCAR-3	-5.55		-5.11		> -4.00	
OVCAR-4	-4.86		-4.58		-4.29	
OVCAR-5	-4.48		-4.32		-4.16	
OVCAR-8	-5.11		-4.53		-4.01	
Renal Cancer						
786-0	-4.61		> -4.00		> -4.00	
A498	-4.71		-4.33		> -4.00	
ACHN	-5.21		-4.72		-4.34	
CAKI-1	-4.51		-4.03		> -4.00	
RXF-393	-4.73		-4.38		-4.03	
RXF-631	-4.69		> -4.00		> -4.00	
SN12C	-4.84		-4.55		-4.27	
TK-10	-4.37		-4.02		> -4.00	
UO-31	-4.52		> -4.00		> -4.00	
MG_MID	-4.85		-4.37		-4.10	
Delta	0.70		0.74		0.27	
Range	1.36		1.11		0.37	

BAD ORIGINAL

National Cancer Institute Developmental Therapeutics Program

TABLE 22 **Mean Graphs** BCH - 688

NSC: D-638339-G/1 | Units: Molar | SSPL: Y71X | Exp. ID: 90I2IS84

Report Date: March 1, 199x | Test Date: December 18, 1990

Panel/Cell Line	Log_{10} GI50	Log_{10} TGI	Log_{10} LC50
Leukemia			
CCRF-CEM	-4.78	-4.28	> -4.00
HL-60(TB)	-4.60	> -4.00	> -4.00
K-562	-4.32	> -4.00	> -4.00
MOLT-4	-4.25	> -4.00	> -4.00
RPMI-8226	-4.26	> -4.00	> -4.00
SR			
Non-Small Cell Lung Cancer			
A549/ATCC	> -4.00	> -4.00	> -4.00
EKVX	-4.42	> -4.00	> -4.00
HOP-62	> -4.00	> -4.00	> -4.00
HOP-92	> -4.00	> -4.00	> -4.00
NCI-H226	> -4.00	> -4.00	> -4.00
NCI-H23			
NCI-H322M	> -4.00	> -4.00	> -4.00
NCI-H460	> -4.00	> -4.00	> -4.00
NCI-H522	-4.56	> -4.00	> -4.00
LXFL-529L	-4.08	> -4.00	> -4.00
Small Cell Lung Cancer			
DMS 114	-4.07	> -4.00	> -4.00
DMS 273	> -4.00	> -4.00	> -4.00
Colon Cancer			
COLO 205	> -4.00	> -4.00	> -4.00
DLD-1	> -4.00	> -4.00	> -4.00
HCC-2998			
HCT-116	-4.11	> -4.00	> -4.00
HCT-15	-4.17	> -4.00	> -4.00
HT29	> -4.00	> -4.00	> -4.00
KM12	> -4.00	> -4.00	> -4.00
KM20L2			
SW-620	> -4.00	> -4.00	> -4.00
CNS Cancer			
SF-268			
SF-295	-4.03	> -4.00	> -4.00
SF-539	-4.37	> -4.00	> -4.00
SNB-19	> -4.00	> -4.00	> -4.00
SNB-75	> -4.00	> -4.00	> -4.00
SNB-78	-4.37	> -4.00	> -4.00
U251	-4.31	> -4.00	> -4.00
XF 498	> -4.00	> -4.00	> -4.00
Melanoma			
LOX IMVI	-4.25	> -4.00	> -4.00
MALME-3M	> -4.00	> -4.00	> -4.00
M14	> -4.00	> -4.00	> -4.00
MI9-MEL	-4.30	> -4.00	> -4.00
SK-MEL-28	> -4.00	> -4.00	> -4.00
SK-MEL-5	-4.07	> -4.00	> -4.00
UACC-257	> -4.00	> -4.00	> -4.00
UACC-62	> -4.00	> -4.00	> -4.00
Ovarian Cancer			
IGROV1	> -4.00	> -4.00	> -4.00
OVCAR-3	-4.11	> -4.00	> -4.00
OVCAR-4	> -4.00	> -4.00	> -4.00
OVCAR-5			
OVCAR-8	-4.12	> -4.00	> -4.00
Renal Cancer			
786-0	-4.23	> -4.00	> -4.00
A498	> -4.00	> -4.00	> -4.00
ACHN	> -4.00	> -4.00	> -4.00
CAKI-1	> -4.00	> -4.00	> -4.00
RXF-393	-4.14	> -4.00	> -4.00
RXF-631	-4.21	> -4.00	> -4.00
SN12C	> -4.00	> -4.00	> -4.00
TK-10	> -4.00	> -4.00	> -4.00
UO-31	-4.02	> -4.00	> -4.00
MG_MID	-4.12	-4.01	-4.00
Delta	0.66	0.28	0.00
Range	0.78	0.28	0.00

+3 +2 +1 0 -1 -2 -3

1778

Example 18

In Vitro Activity of Heteroanthrocyclinones in Cell Lines Displaying Multi Drug Resistance (MDR)

The anticancer activity of heteroanthracyclinones and heteroanthracyclines from this invention was confirmed from a second independent assay. This biological study was carried out at the Oncology department of the faculty of medicine at McGill University, in Montreal, Canada. It involved the use of adriamycin sensitive cells lines as well as multidrug resistant ones. The following describes the methodology used for anticancer testing. Biological results follow the protocol.

SCREENING TEST

For the IN VITRO test, we chose a tumor clonogenic assay which measures the ability of tumoral cells to form colonies (multicellular growth units) as a result of cell division in semisolid agar support (2,3). A more elaborate version of this fundamental assay, the soft agar colony formation disk diffusion assay was used. This assay defines the relative activity of one particular drug versus a tumoral cell line type. The effect of the test drug against tumoral cells could be measured by its inhibitory capacity against colony formation after the delivery of the compound, in different concentrations on an filter disk(4).

COLONY FORMATION DISK DIFFUSION ASSAY

A modified technique of this assay was used in order to investigate the antiproliferative activity of candidate compounds. Tumoral cells from solid tumors and ascitic lines were plated separately in a two layer agar matrix. Cell lines to be tested were suspended in an upper layer of 0.4% Noble agar (Difco#00142-01) in RPMI-1066 (Gibco#3201875) at a yield varying between 10^4 to 2 X 10^5 cells per 60 mm Petri dish. Plating efficiency was determined for each line in order to achieve an optimal number of colonies per dish. Plates were examined before drug administration to confirm a uniform dispersion of single cells. The bottom layer consisted of 0.8% Noble agar, 0.8% Tryptic Soy Broth (difco#0037001) in CMRL-1066/Fischer's. The bottom layers were used within 2 and 9 days of preparation. Plated dishes (bottom layer of agar, upper layer of cells and administered drug were incubated in humidified atmosphere at 37°C, 5% CO_2 for 10-20 days depending upon the time necessary to observe adequate colonies (defined as a cell aggregate of more than 50 cells) both control and drug inhibited. Drugs were administered on a paper filter disk (Whatman No. 1) of 6.5 mm diameter placed on the upper layer at 1/3 distance from the edge of the dish. The anti-clonogenic activity of the compounds was measured as the zone of inhibition from the disk edge to the most proximal colonies. This zone of inhibition was checked on an inverted microscope (40X) and was measured with a micrometer mounted in the eyepiece. The ocular micrometer was calibrated with a stage micrometer set for a particular combination of ocular and objective lenses.

Our calibration values were converted to those already used in other laboratories in order to have comparable values. 200 units of activity are equivalent to 6.5mm distance from the disk edge to the first colonies (5). Each concentration was run in triplicate and dispersion of

the values was surprisingly small for the type of biological tests. We made a modification of the initial technique by not plating a solid tumor and a leukemia simultaneously in the same Petri dish. Anti-clonogenic tests performed on leukemia cell line have helped in the discovery of the majority of current clinically used cytostatic drugs. Our tests on solid tumor lines (animal or human) may help define active compounds with solid tumor specificity. This specific activity would be indicated by a higher level of cloning inhibition in solid tumors versus leukemias (6).

MATERIALS AND METHODS

CELL LINES: 5 murine tumor lines and 2 rat tumor lines and 5 human tumor lines were used (Table 1).

ANIMAL TUMORS: 2 transplantable solid tumors, one reticulum cell sarcoma and one leukemia with and ADR resistant form were passaged IN VIVO. P388 and P388/ADR (7) routinely passaged in DBA/2, M5076 (8), B16 melanoma (9), Lewis lung carcinoma (9) routinely passaged in C57B1/6, were supplied by NCI, DCT Tumor Repository, NCI-FCRF, Frederick, MD. Rat breast carcinoma MATB WT (18) and MATB/ADR (18) obtained from the Oncology Dept. of the Montreal General Hospital were passaged IN VITRO. Murine tumors were maintained IN VIVO in order to diminish the selection of subpopulations of cells normally present in the heterogenous IN VIVO tumor. The actual drug sensitivity assay was done IN VITRO. For these experiments cells from freshly excised tumors or from ascitic fluids were maintained in RPMI-1066.

MICE: Inbred C57B1/6 females and DBA/2 females (20±2g) were obtained from Charles River Laboratory, Que. and used as tumor recipient.

CELL PREPARATION. The protocol described by Corbett et al (6) was used. Tumors were excised aseptically from the host and cut in 200-300 mg fragments in HBSS (Gibco# 3104020). The fragmented tumor was forced through a 60 mesh sieve and the sieve rinsed twice with cold HBSS. The cell suspension was gently centrifuged (100-150) g/5 min), resuspended in HBSS and once again centrifuged. The cell pellet was finally suspended in an adequate volume of medium. Difficult to disrupt tumors were digested with 0.25% Trypsin EDTA (Gibco#6105305). The viability was over 90% for all cell lines prior starting experiments except for the LL line and P399/ADR which showed a varying degree of viability between 40 and 60%.

HUMAN TUMORS. MCF7 (10) and MCF7/ADR(11) HT29(12) were obtained from NCI, DCT Tumor Repository, NCI-FCRF, Frederick, MD. LS180 (13) and BE-1(14) were obtained from the Oncology Dept. of the Montreal General Hospital. Cell lines were initially maintained in RPMI-1640 supplemented with 10% fetal bovine serum and 100 units of Penicillin-Streptomycin (Gibco#6005140). Cell lines were routinely passaged twice a week by trypsinization and maintained in 25, or 75-sq. cm Falcon Plastic flasks at 37°C, 5% CO_2 in humidified atmosphere.

DRUGS: Doxorubicin hydrochloride available from a commercial source was used as an internal control. For some line the DOX control was run simultaneously for both new synthesised agents. Our values for DOX as an internal

control were consistently in accord with references(15,16).

Both compounds were dissolved in DMSO (1 mg/100ul) and brought to final volume (250ul) with Millipore deionized sterile water. Further dilutions were made with Milliwater. A volume of 25 ul of freshly prepared solution was placed on the filter disk and allowed to dry. A second control with vehicle (DMSO /Milliwater) was run simultaneously. Control disks with vehicle were found to produce no zone of inhibition. For the determination of drug action the compounds were tested in serial ten-fold dilutions. The results were expressed as units of inhibition of colony formation (Zone Units) produced at the same mass concentrations as DOX. Dilutions of the compounds as well as of DOX were stored in sterile Cryovials (Gibco#366656) at -20°C for no longer than 3 days.

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BIOLOGICAL RESULTS

The results obtained with the tumor clonogenic assay, in which a semisolid agar support was used, confirm the antitumor activity of the heteroanthracyclinones and heteroanthracyclines described herein (tables 23 and 24). In the human breast cancer lines, MCF7 and MCF7/ADR, a similar level of activity occurred for BCH's:687, 692, 699, 700, 701 and 706 between both cell lines, indicating a lack of cross resistance with adriamycin (Table 23). Most notably is the fact that BCH-684 and 712 were more active in the adriamycin resistant cell line, MCF7/ADR, than in the sensitive one. Similar results were obtained with the rat breast tumor cell lines MATB.WT and MATB/ADR. In this case BCH's: 677, 681, 684, 700, 705 and 712 displayed no cross resistance with adriamycin in MATB; BCH's: 704, 710 and 711 displayed a greater cytotoxicity in the resistant breast tumor cell line, MATB/ADR, than in the sensitive line. The results obtained with the breast tumor lines indicate that the heteroanthracyclinones and heteroanthracyclines of the present invention operate via an advantageous cytotoxic mechanism. A range of activity was observed from the compounds described herein in this example. The most active were BCH's: 684, 687, 691, 692, 700, 704, 706 and 710. BCH 710 shows specificity for the MATB/ADR rat breast ADR resistant adenocarcinoma and mouse ovarian reticulum cell sarcoma. Specificity for breast cancer was demonstrated by BCH's 700 and 704. Good broad spectrum activity was observed from BCH's: 684, 691, and 692, except in the leukemic cell lines P388 and P388/ADR, confirming the specificity of these compounds for solid tumors. Human colon adenocarcinoma HT-29, LS180 and BE1 responded well with BCH-687, an analog in which no benzylic

substituents are present. This is noteworthy because analogous compounds in the field of anthracyclines are normally not significantly cytotxic towards tumor cells.

The data presented in this example supports the results presented in examples 15, 16 and 17. Heteroanthracyclinones and heteroanthracyclines, with an heteroatom in ring A as described herein, display a range of antineoplastic activity with specificity towards solid tumors. Cross resistance with doxorubicin or dannorubicin in some cases is not observed. The fact that cytotoxicity in hematologic malignancies is low in comparison with solid tumors suggest that myeclotoxicity should be decreased. This recurrent feature suggests that the therapeutic index of the compounds of the present invention has been increased. Therefore compounds of the present invention should be clinically useful because of reduced bone marrow toxicity and because of their demonstrated activity towards some resistant tumor cell lines.

TABLE 23

CONCENTRATION: 10μG/DISK

	MCF7	MCF7/ADR	HT29	LS180	BE-1	MATB.WT	MATB/ADR	P388	P388/ADR	M5076	B16	LL
BCH-651	0a)	10.0± 5.0	0	0	0	0	0	45.7±12.9	10.0± 0.0	15.2± 4.3	0	-
BCH-654	0	0	0	24.4± 8.6	24.4± 8.6	0	0	0	0	0	0	-
BCH-658	0	0	0	48.8±34.5	0	0	0	42.7±17.2	18.3± 8.6	26.6±13.6	0	-
BCH-660	27.4± 4.3	9.1± 4.3	27.4± 4.3	15.0± 4.2	45.7±21.5	137.2±21.5	24.4± 8.6	18.3± 8.6	6.1± 8.6	24.4± 8.6	6.1± 8.6	-
BCH-674	0	0	122.2±80.6	0	-	30.5±13.0	24.4± 8.6	30.5±25.8	0	-	91.5±60.3	54.9± 8.6
BCH-675	0	0	0	0	0	0	22.3± 3.5	0	10.1± 9.3	0	0	75.2±40.5
BCH-681	-b)	82.7±30.1	106.7±21.5	-	-	51.8± 4.3	54.9± 8.6	-	-	-	-	-
BCH-684	115.9± 8.6	161.6±30.1	137.2±21.5	-	-	131.3±12.9	122.0±17.0	-	-	-	-	-
BCH-687	71.1± 9.3	61.0± 6.1	61.0±12.2	152.5±30.5	85.0±44.2	42.7± 6.1	69.1± 7.0	81.3±30.0	0	0	34.6± 3.6	62.8±30.7
BCH-691	186.5± 4.9	115.5± 9.1	137.0±21.2	148.5± 4.9	55.0±10.0	120.0±50.5	0	100.5±50.0	50.0±10.0	120.0±28.8	114.0±30.2	50.6±25.5
BCH-692	131.0±12.7	122.0±10.0	105.0± 5.0	130.0±12.5	0	150.0±18.5	0	50.5±10.9	25.0±10.0	50.0±25.5	0	80.5±20.5
BCH-693	0	24.4±17.2	0	0	0	0	0	120.0± 0.0	20.0± 0.0	27.4± 4.3	0	-
BCH-694	61.0± 0.0	0	30.5± 8.6	48.8±17.2	54.9± 8.6	76.2± 2.5	27.4± 4.3	67.1± 8.6	6.1± 8.6	27.4± 4.3	0	-
BCH-704	183.0±10.8	122.0±25.8	39.6±12.9	38.3± 2.4	-	198.5±21.9	320.2±64.7	-	-	-	-	-
BCH-706	103.7±25.5	91.5± 8.6	-	-	-	-	-	-	-	-	-	-
BCH-710	0	0	30.0± 8.4	48.5±26.1	-	44.0	288.0±21.9	13.0± 0.0	0	209.5±21.9	21.0± 2.1	-
BCH-711	0	24.4± 8.5	27.0± 4.2	18.0±16.9	-	27.0± 4.2	45.5±21.9	45.5±21.9	40.0±20.0	55.0± 8.4	27.0± 4.2	-
BCH-712	0	24.0± 8.4	0	9.0± 4.2	-	21.0± 4.3	0	6.1± 0.0	0	0	0	-
BCH-713	0	24.0± 8.6	0	0	-	0	0	0	0	0	0	-
BCH-714	0	0	0	9.0± 4.2	-	0	0	0	0	15.5± 5.0	0	-
BCH-717	0	0	0	0	-	0	0	0	0	18.3	0	-
BCH-721	55.0± 8.4	91.0±86.2	55.5± 8.0	18.9	-	33.0± 4.2	45.5±21.9	45.5±21.9	21.0±21.2	78.0±18.3	76.0±21.2	-

a) Zone Units, 200 units of activity represents 6.5mm of a clear zone from the disk edge.
b) Compounds were not tested in cell lines with a slash indicated above.

TABLE 24

CONCENTRATION: 100μG/DISK

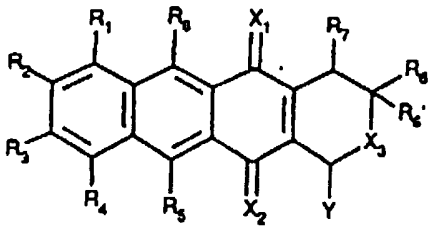
	MCF7	MCF7/ADR	HT29	LS180	BE-1	MATB.WT	MATB/ADR	P388	P388/ADR	M5076	B16	LL
BCH-651	115.9± 8.6	131.1± 30.1	61.0± 1.0	76.2±21.5	106.7±21.5	36.6± 8.6	100.0	294.5±101.1	30.5± 8.6	51.3± 43.3	27.5±13.4	27.4± 4.3
BCH-653	106.1±21.5	91.5± 43.1	42.7± 8.6	35.5± 0.7	76.2±21.5	0	0	64.0± 4.2	66.8± 8.2	85.4± 25.8	0	18.3± 0.0
BCH-654	115.9± 8.6	155.6± 12.7	106.5±21.9	158.5± 9.1	153.0± 1.4	152.5± 25.8	134.3± 17.3	0	0	0	137.4±21.8	0
BCH-658	0a)	0	0	164.7±25.8	0	0	0	61.0± 0.0	51.3±20.7	76.2± 21.5	0	51.9±21.5
BCH-660	82.3±12.9	109.8± 10.0	103.7± 2.1	76.0± 4.2	125.0±12.7	137.2± 21.5	161.5± 30.4	54.9± 0.0	54.9± 8.6	61.0± 0.0	85.4± 8.6	55.0± 8.4
BCH-674	76.2±21.6	339.6± 4.3	36.6±17.2	67.1± 8.6	-	198.2± 21.5	213.5± 25.8	137.2± 38.8	150.0± 8.0	-	122.0±86.2	115.9± 8.0
BCH-675	30.5±10.5	26.3± 14.0	0	148.4±31.3	46.7± 5.3	32.5± 9.3	59.4± 8.6	152.5± 30.5	146.3±32.3	142.0± 35.2	0	264.0±38.0
BCH-681	-	326.3± 56.0	213.5±43.1	-	-	176.9± 8.6	244.0± 43.1	-	-	-	-	-
BCH-684	225.7±25.8	437.1± 30.1	170.8±86.2	-	-	366.0±172.5	320.2±107.8	-	-	-	-	-
BCH-687	152.5±50.0	140.0± 32.3	150.4±25.3	233.8±17.6	162.6±70.4	97.6± 20.0	101.6± 35.2	183.0± 81.0	153.6±30.6	410.8± 46.5	70.1±13.0	182.6± 35.2
BCH-691	417.5±99.7	213.5± 43.1	198.0±21.2	287.0±80.3	155.5±50.3	380.0±120.0	200.0± 95.0	200.2± 50.0	98.0±15.0	220.0± 50.8	250.0±58.0	180.0±120.0
BCH-692	289.5±22.0	237.9± 8.6	181.5± 2.1	250.0± 8.4	100.0±50.0	400.5±100.0	180.0± 50.5	180.0± 50.6	150.5±50.0	200.0±100.0	200.0±55.0	140.3± 40.5
BCH-693	67.1±34.5	67.1± 25.8	39.6± 4.3	39.6± 4.3	76.2±21.5	42.7± 8.8	67.1± 8.6	400.0	76.5±21.9	51.8± 12.9	27.4± 4.3	45.7±21.5
BCH-694	149.4±12.9	161.5± 13.4	143.3±30.1	153.2± 1.0	189.0± 8.4	207.0± 33.9	213.5± 43.1	115.9± 94.8	39.6±12.9	137.2± 99.2	128.0±26.0	30.5± 8.6
BCH-704	320.5±21.5	323.0± 16.8	152.5±43.1	131.1±31.1	-	414.8± 25.8	527.4± 72.9	-	-	-	-	-
BCH-705	79.3± 8.6	35.5± 7.3	-	-	-	259.2± 21.5	155.5± 4.3	-	-	-	-	-
BCH-706	213.5±43.1	183.0	-	-	-	-	-	-	-	-	-	-
BCH-710	24.0± 8.4	106.0± 21.9	69.0±30.0	110.0±50.2	-	366.0± 0.0	350.0± 64.3	326.5± 43.1	110.0± 0.0	533.0±20.0	21.0± 2.1	-
BCH-711	244.0±17.2	222.4±159.2	91.5±43.1	182.5±43.1	-	137.0± 21.2	107.0± 21.9	183.0± 0.0	150.0±30.0	198.0±21.2	137.0±21.2	-
BCH-712	54.5± 9.1	79.0± 8.4	55.0± 8.4	158.0±34.6	-	76.0± 21.2	64.0± 4.2	70.0± 21.2	42.5± 9.1	158.0±34.6	27.0± 4.2	-
BCH-713	0	94.5± 64.7	0	45.7±21.5	-	27.4± 4.3	0	45.7± 21.5	61.0± 0.0	42.7± 8.6	24.4± 8.6	-
BCH-714	0	0	0	42.0±26.0	-	0	0	27.0± 4.2	0	55.0± 8.4	0	-
BCH-717	0	0	0	61.0± 0.0	-	0	0	122.0± 0.0	0	39.5±30.4	106.0±64.3	-
BCH-721	167.0±21.9	183.0± 86.2	121.5±43.1	122.0± 0.0	-	143.0± 12.7	137.0± 21.2	137.0± 21.2	183.0±86.2	259.0±21.2	198.0±21.2	-

a) Zone units, 200 units of activity represents 6.5mm of a clear zone from the disk edge.
b) Compound were not tested in cell lines with a slash indicated above.

WE CLAIM:

SAVING NOW PARTICULARLY DESCRIBED AND ASCERTAINED MY/OUR SAID INVENTION AND IN WHAT MANNER THE SAME IS TO BE PERFORMED, I/WE DECLARE THAT I/WE CLAIM IS:-

1. A compound of the formula



Wherein,

X_1 and X_2 are independently selected from the group consisting of

O,

S,

C=N(R), wherein R is selected from the group consisting of

hydrogen,

C_{1-16} alkyl,

C_{1-16} acyl and,

C_{1-16} alkylamine,

X_3 is selected from the group consisting of

O,

S,

SO,

SO_2,

NO, and

NR, wherein R is selected from the group consisting of

C_{1-16} acyl,

C_{1-16} alkyl,

C_{1-16} aryl,

C_{1-16} haloacyl, and

hydrogen;

R_1, R_2, R_3, R_4, R_5 and R_8 are independently selected from the group consisting of

hydrogen,
hydroxyl,
C_{1-16} alkyl,
C_{1-16} alkoxyl,
C_{3-8} cycloalkyl,
tosyl,
triflate,
trifluoroacetate,
halogen,
nitro,
cyano,
C_{1-16} acyl,
C_{1-16} arylacyl,

aminoalkylaminoalcohol of formula $NH(CH_2)_nNH(CH_2)_mOH$ where n and m independently range from 1 to 4,
aminoalkylaminoalkylhalide of formula $NH(CH_2)_nNH(CH_2)_mX$ where n and m independently range from 1 to 4 and X is a halogen,
amino which may be unsubstituted or mono- or di-substituted by C_{1-8} alkyl, C_{3-8} cycloalkyl, acyl, trifluoroacyl, aralkyl or aryl, C_{1-8} alkenyl, C_{1-8} alkynyl,
halaoalkylnitrosureido of the formula $NH(CO)N(NO)(CH_2)_nCH_2X$, wherein n is 0 to 4 and X is a halogen,
thiol, and
a group of the formula -O-C(R)=O wherein R is selected from the group consisting of

hydrogen,
C_{1-16} alkyl,
C_{3-8} cycloalkyl,

alkoxyalkyl,
aralkyl,
araloxyalkyl,
aryloxyalkyl and
aryl;

R_6 is selected from the group consisting of
hydrogen,
C_{1-16} alkyl,
C_{3-8} cycloalkyl,
acyl of the formula -C(R)=O, or its dioxolane or dioxane ketal wherein R is selected from the group consisting of
hydrogen,
C_{1-16} alkyl,
C_{3-8} cycloalkyl,
hydroxyalkyl,
alkoxyalkyl,
araloxyalkyl,
acyloxyalkyl,
amino which may be unsubstituted or mono- or di-substituted by C_{1-8} alkyl,
C_{3-8} cycloalkyl, acyl, trifluoroacyl,
aralkyl or aryl, and
a naturally occurring amino acid, for example alanine, arginine, cysteine, glycine, leucine, lysine, methionine and the like, or a synthetic amino acid;
a group of the formula $-C(R)(OC_{1-5}\ alkyl)_2$ wherein R is as defined above
a group of the formula -C(OR)=O, wherein R is selected from the group consisting of
hydrogen,
C_{1-16} alkyl,
C_{3-8} cycloalkyl,
hydroxyalkyl,
alkoxyalkyl,

aryloxyalkyl,
araloxyalkyl,
aryl and
aralkyl;

a group of the formula $-CH_2C(OR)=O$, wherein R is selected from the group consisting of

hydrogen,
C_{1-16} alkyl,
C_{3-8} cycloalkyl,
hydroxyalkyl,
alkoxyalkyl,
aryloxyalkyl,
araloxyalkyl,
aryl,
aralkyl, and
amino, which may be unsubstituted, mono- or di-substituted by C_{1-8} alkyl, C_{3-8} cycloalkyl, acyl, trifluoroacyl, aralkyl or aryl;

R_6' is selected from the group consisting of

hydrogen,
C_{1-16} alkyl,
halogen,
amino,
hydroxy,
C_{1-16} alkoxy,
thiol,
cyano,
sulfide,
acyl of the formula $-C(R)=O$, wherein R is selected from the group of

hydrogen,
C_{1-16} alkyl,
C_{3-8} cycloalkyl,
hydroxyalkyl,
araloxyalkyl,
alkoxyalkyl,
acyloxyalkyl,
amino which may be unsubstituted or mono- or di-substituted by C_{1-8} alkyl, C_{3-8} cycloalkyl, acyl, trifluoroacyl, aralkyl or aryl, and a naturally occuring amino acid, for example alanine, arginine, cysteine, glycine, leucine, lysine, methionine and the like, or a synthetic amino acid;

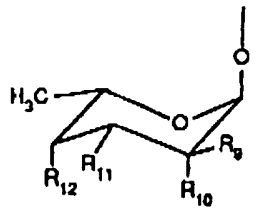
A group of the formula -C(OR)=O, wherein R is selected from the group consisting of
hydrogen,
C_{1-16} alkyl,
C_{3-8} cycloalkyl,
hydroxyalkyl,
alkoxyalkyl,
aryloxyalkyl,
araloxyalkyl,
aryl and
aralkyl;
C_{1-16} alkenyl

Y and R_7 are independently selected from the group consisting of
hydrogen,
halogen,
hydroxyl,
C_{1-16} alkoxyl,

C_{1-16} alkyl,
C_{2-16} acetylenyl,
C_{3-8} cycloalkyl,
C_{2-16} alkenyl,
cyano,
a group of the formula -O-C(R)=O, wherein R is selected from the group consisting of
hydrogen,
C_{1-16} alkyl,
C_{3-8} cycloalkyl, and
alkoxyalkyl,
aryl;
an acyl of the formula -C(R)=O, wherein R is selected from the group consisting of
hydrogen,
thiol,
C_{1-16} thioalkyl,
C_{1-16} alkyl,
C_{3-8} cycloalkyl,
hydroxyalkyl,
alkoxyalkyl,
araloxyalkyl,
acyloxyalkyl,
amino which may be unsubstituted or mono- or di-substituted, and a naturally occurring amino acid as defined above or a synthetic amino acid;
a group of the formula -C(OR)=O, wherein R is selected from the group consisting of
hydrogen,
C_{1-16} alkyl, and
C_{3-8} cycloalkyl; and
mono or oligosaccharides commonly present in

other anthracyclines, for example one or more sugars selected from rhodosamine, cinerulose-B, L-cinerulose, D-cinerulose, cinerulose-A, amicetose, aculose, rednose, rhodinose, 2-deoxyfucose,

and a saccharide of the formula



wherein

R_9 and R_{10} are independently selected from the group consisting of

hydrogen,
halogen,
hydroxy,
acetoxy,
C_{1-16} alkoxy,
C_{1-16} alkyl,
C_{3-8} cycloalkyl, and
thiol;

R_{11} is selected from the group consisting of

amino, which may be unsubstituted or mono or di-substituted by C_{1-8} alkyl, C_{3-8} cycloalkyl, acyl, trifluoroacyl, aralkyl or aryl and a naturally occuring amino acid, for example alanine, arginine, cysteine, glycine, leucine, lysine, methionine and the like, or a syntehtic amino acid;
mono or dibenzylated amino,
acylated amino,
trifluoroacylated amino,

morpholino,
cyano substituted morpholino,
mono-, di-, tri- or tetra-methoxy substituted morpholino,
mono-, di, tri-or tetra-acetoxy substituted morpholino,
hydroxyl,
hydrogen,
halogen,
acetoxy,
C_{1-16} alkoxyl,
C_{3-8} cycloalkyl,
thiol,
sulfide,
a group of the formula $NH(CH_2)_NCH(OR)_2$, wherein R is independently selected from the group consisting of a C_{1-16} alkyl, C_{1-16} acyl or C_{7-16} aroyl and wherein n is 0 to 5,
chloroalkylnitrosoureido of the formula $NH(CO)N(NO)(CH_2)_nCH_2Cl$, wherein n is 0 to 4;

R_{12} is selected from the group consisting of
hydrogen,
hydroxyl or its tetrahydropranyl ether (-OTHP),
halogen,
mono or oligosaccharides commonly present in other anthracyclines such as those defined above for R_7,
amino,
mono or dialkylated amino in which each alkyl contains 1 to 16 carbon atoms,
C_{1-16} alkoxy,
C_{3-8} cycloalkyl,

benzoate which may be unsubstituted or substituted with nitro, for example
p-nitrobenzoate,
acetoxy, and
trifluoroacetoxy.

chloroalkyl-nitrosoureido as defined above for R_{11} inclusive of isomers and mixtures thereof, including diastereoisomeric mixtures and racemic mixtures, tautomeric forms and the pharmaceutically acceptable salts and metal chelate complexes.

2. A compound according to claim 1, wherein
X_1, and X_2 are independently selected from the group consisting of
O,
S, and
NH;
X_3 is selected from the group consisting of
O,
S,
SO,
SO_2,
NH, and
NO;
R_1, R_2, R_3, R_4, R_5 and R_8 are independently selected from the group consisting of
hydrogen,
hydroxyl,
C_{1-4} alkoxyl,
tosyl,
triflate,
fluorine,

chlorine,
aminoalkylaminoalcohol of formula $NH(CH_2)_nNH(CH_2)_mOH$ where n and m independently
range from 1 to 3,
aminoalkylaminoalkylchloride of formula $NH(CH_2)_nNH(CH_2)_mCl$ where n and m independently range from 1 to 3.
amino,
chloroalkylnitrosoureido of the formula $NH(CO)N(NO)(CH_2)_n CH_2 Cl$, wherein n is 0 to 4, and
a group of the formula -O-C(R)=O, wherein R is selected from the group consisting of
hydrogen,
C_{1-6} alkyl,
and aryl;

R_6 is selected from the group consisting of
hydrogen,
C_{1-4} alkyl,
acyl of the formula -C(R)=O, wherein R is selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
hydroxylalkyl,
alkoxyalkyl,
acyloxyalkyl and
amino which may be unsubstituted or mono- or di-substituted with C_{1-8} alkyl, C_{3-8} cycloalkyl, acyl, trifluoroacyl, aralkyl or aryl;
a group of the formula -C(OR)=O, wherein R is selected from the group consisting of
hydrogen,

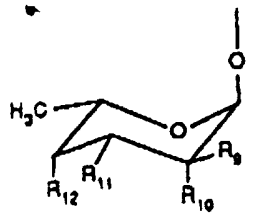
C_{1-8} alkyl,
aryl,
aralkyl; and

a group of the formula $-CH_2C(OR)=O$, wherein R is selected from the group consisting of
hydrogen,
straight or branched C_{1-8} alkyl, and
amino which may be unsubstituted
or mono · or di-substituted with
C_{1-8} alkyl, C_{3-8} cycloalkyl, acyl,
trifluoroacyl, aralkyl or aryl;

R_6' is selected from the group consisting of
hydrogen,
fluorine,
amino,
C_{1-4} alkoxy,
sulfide,
acyl of the formula $-C(R)=O$, where R is selected from the group of
hydrogen,
C_{1-8} alkyl,
hydroxyalkyl,
acyloxyalkyl,
amino,
cyano,
a group of the formula $-C(OR)=O$, wherein R is selected from the group consisting of
hydrogen,
C_{1-8} alkyl,
aryl,
C_{1-8} alkenyl;

Y and R_7 are independently selected from the group consisting of

hydrogen,
halogen,
hydroxyl,
C_{1-8} alkoxy,
C_{2-8} acetylenyl,
C_{2-8} alkenyl,
cyano,
a group of the formula -O-C(R)=O, wherein R is selected from the group consisting of
hydrogen, and
C_{1-8} alkyl;
acyl of the formula -C(R)=O, wherein R is selected from the group consisting of
hydrogen,
thiol,
C_{1-8} alkyl,
hydroxyalkyl,
amino;
a group of the formula -C(OR)=O, wherein R is selected from the group consisting of
hydrogen, and
C_{1-8}alkyl,
and a saccharide of formula



wherein
R_9 and R_{10} are independently selected from the group consisting of
hydrogen,

fluorine,
chlorine, and
hydroxyl;

R_{11} is selected from the group consisting of
amino which may be unsubstituted or mono- or di-substituted with C_{1-8} alkyl, C_{3-8} cycloalkyl, acyl, trifluoroacyl, aralkyl or aryl;
morpholino,
cyano substituted morpholino,
mono-, di-, tri-, or tetra-methoxy substituted morpholino,
hydroxyl,
mono or dialkylated amino with 1 to 16 carbons,
C_{1-8} alkoxyl,
a group of the formula $NH(CH_2)_nCH(OR)_2$ wherein R is independently selected from a group consisting of C_{1-8} alkyl, C_{1-8} acyl or C_{7-12} aroyl and wherein n is 1 to 5,
chloroalkylnitrosoureido of the formula $NH(CO)N(NO)(CH_2)_nCH_2Cl$ wherein n is 0 to 4, and
fluorine; and

R_{12} is selected from the group consisting of
hydroxyl or its tetrahydopyranyl ether,
halogen,
mono or oligosaccharide commonly present in other anthracyclines, for example one or more sugars selected from rhodosamine, cinerulose-B, L-cinerulose, D-cinerulose, cinerulose A, amicetose, aculose, rednose, rhodinose, 2-deoxyfucose, daunosamine and

trifluoroacetyldaunosamine,
amino,
mono or dimethylated amino,
C_{1-8} alkoxy,
benzoate,
p-nitrobenzoate,
acetoxy and
trifluoroacetoxy.

inclusive of isomers and mixtures thereof, including diastereoisomeric mixtures and racemic mixtures, tautomeric forms and the pharmaceutically acceptable salts and metal chelate complexes.

3. A compound according to claim 1, wherein
X_1, and X_2, are independently selected from the group consisting of
O, and
NH;
X_3 is selected from the group consisting of
O,
S,
SO,
NH,
NO;
R_1, R_2, R_3, R_4, R_5 and R_8 are independently selected from the group consisting of
hydrogen,
hydroxy,
methoxy,
aminoethylaminoethanol
aminoethylaminoethylchloride
chloroalkylnitrosoureido of the formula

$NH(CO)N(NO)(CH_2)_nCH_2Cl$, wherein n is 0 to 2,
amino, and
fluorine;

R_6 is selected from the group consisting of
C_{1-4} alkyl,
acyl of the formula -C(R)=O, wherein R is selected from the group consisting of
methyl,
hydroxymethyl,
acyloxymethyl and
amino;
a group of the formula -C(OR)=O, wherein R is selected from the group consisting of
hydrogen,
methyl and
ethyl;
a group of the formula $-CH_2C(OR)=O$, wherein R is selected from the group consisting of
hydrogen,
methyl and
ethyl;
R_6' is selected from the group consisting of
hydrogen,
fluorine,
amino,
methoxy,
acyl of the formula -C(R)=O, wherein R is selected from the group of
hydrogen,
C_{1-5} alkyl,
hydroxyalkyl,
amino,

cyano,

a group of the formula -C(OR)=O, wherein R is selected from the group consisting of

hydrogen,

C_{1-5} alkyl,

aryl,

C_{1-4} alkenyl;

Y and R_7 are independently selected from the group consisting of

hydrogen,

halogen,

hydroxy,

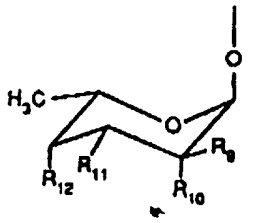
methoxy,

cyano,

acetate,

acetyl and

a saccharide of formula



wherein

R_9 and R_{10} are independently selected from the group consisting of

hydrogen and

fluorine;

R_{11} is selected from the group consisting of

amino,

dimethylamino,
trifluoroacetamido,
morpholino,
cyano substituted morpholino,
mono-, di-, tri-, or tetra-methoxy substitiuted morpholino,
a group of the formula $NH(CH_2)_nCH(OR)_2$ wherein R is selected from a group consisting of C_{1-4} alkyl C_{1-4} acyl or C_{7-8} aroyl and wherein N is 2 to 5,
chloroalkylnitrosoureido of the formula $NH(CO)N(NO)(CH_2)_nCH_2Cl$, wherein n is 0 to 4, and
hydroxyl; and

R_{12} is selected from the group consisting of
hydroxyl or its tetrahydopyranyl ether,
benzoate,
p-nitrobenzoate,
amino, and
fluorine.

inclusive of isomers and mixtures thereof, including diastereoisomeric mixtures and racemic mixtures, tautomeric forms and the pharmaceutically acceptable salts and metal chelate complexes.

4. A compound according to claim 1, wherein
X_1 and X_2 are both oxygen;
X_3 is selected from the group consisting of
O,
S,
SO,
NH,

NO;

R_1, R_2, R_3 and R_4 each are hydrogen;

R_5 and R_8 are independently selected from the group consisting of
hydrogen,
hydroxyl,
amino,
aminoethylaminoethanol,

R_6 is selected from the group consisting of
methyl,
ethyl,
acyl of the formula -C(R)=O, or its dioxolane or dioxane ketal wherein R is selected from the group consisting of
methyl,
hydroxymethyl,
acetoxymethyl, and
amino;
a group of the formula C(OR)=O, wherein R is selected from the group consisting of
hydrogen and
methyl; and
a group of the formula $-CH_2C(OR)=O$, wherein R is selected form the group consisting of
hydrogen and
methyl;

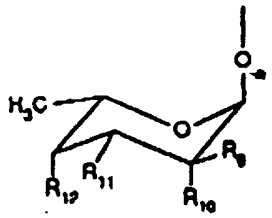
R_6' is selected from the group consisting of
hydrogen,
fluorine,
amino,
cyano, and

a group of the formula -C(OR)=O, wherein R is selected from the group consisting of

C_{1-4} alkyl,

Y and R_7 are independently selected from the group consisting of

hydrogen,
hydroxyl,
bromine,
chlorine,
cyano,
acetate,
acetyl and
a saccharide of formula



wherein

R_9 and R_{10} are independently selected from

hydrogen and
fluorine;

R_{11} is selected from

amino,
dimethylamino,
trifluoroacetamido,
morpholino,
cyano substituted morpholino,
mono-, di-, tri- or tetra-methoxy substituted morpholino and
a group of the formula $NH(CH_2)_NCH(OR)_2$ wherein R is selected from a group consisting of methyl, acyl or benzoyl

N is 3 to 5,

chloroalkylnitrosoureido of the formula $NH(CO)N(NO)(CH_2)_nCH_2Cl$, wherein n is 0 to 4, and

R_{12} is selected from hydroxyl, benzoate and p-nitrobenzoate,

inclusive of isomers and mixtures thereof, including diastereoisomeric mixtures and racemic mixtures, tautomeric forms and the pharmaceutically acceptable salts and metal chelate complexes.

5. The compound of claim 1 which is (1'S,1R,3S) or (1'S,1S,3R) methyl [11-hydroxy-1-(2', 3', 6'- trideoxy-3'-trifluoroacetamido-L-lyxohexopyranose)- 5,12-dioxo-3, 4, 5, 12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

6. The compound of claim 1 which is Ethyl [11-acetoxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

7. The compound of claim 1 which is (1S, 3S) or (1R, 3R) Ethyl [11-acetoxy-1-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

8. The compound of claim 1 which is (1'S,1R,3S) or (1'S,1S,3R) Ethyl[11-acetoxy-1-(2',3',6'-trideoxy-3'-trifluoroacetamido-4'-O-p-nitrobenzoyl-L-lyxohexopyranose)-5,12-dioxo-3,4,5,12-tetrahydroanthranceno [2,3-c] pyran-3-yl] formate.

9. The compound of claim 1 which is (1'S,1R,3S) or (1'S,1S,3R) Methyl[6-acetoxy-1-(2',3',6'-trideoxy-3'-trifluoroacetamido-4'-O-p-nitrobenzoyl-L-lyxohexopyranose)-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

10. The compound of claim 1 which is Methyl [6-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

11. The compound of claim 1 which is Methyl [11-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

12. The compound of claim 1 which is Methyl [6-acetoxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

13. The compound of claim 1 which is Methyl [11-acetoxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

14. The compound of claim 1 which is (1S,3S) or (1R,3R) Methyl [6-acetoxy-1-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

15. The compound of claim 1 which is Ethyl [11-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

16. The compound of claim 1 which is Ethyl [11-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

17. The compound of claim 1 which is Ethyl [6-acetoxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

18. The compound of claim 1 which is (1S,3S) or (1R,3R) Ethyl [6-acetoxy-1-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

19. The compound of claim 1 which is Ethyl (5, 12-dihydroxy-6,11-dioxo,3,4,6,11-tetrahydroanthraceno [2, 3-C] pyran-3-yl) formate.

20. The compound of claim 1 which is (1'S,1R,3S) or (1'S,1S,3R) Ethyl[6-acetoxy-1-(2',3',6'-trideoxy-3'-trifluoroacetamido-4'-O-p-nitrobenzoyl-L-lyxohexopyranose)-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

21. The compound of claim 1 which is Ethyl [6-acetoxy-11-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

22. The compound of claim 1 which is Ethyl [6-hydroxy-11-acetoxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

23. The compound of claim 1 which is Ethyl [6,11-diacetoxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

24. The compound of claim 1 which is (1S,3S) or (1R,3R) Ethyl [11-acetoxy-1,6-dihydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

25. The compound of claim 1 which is (1'S,1S,3R) or (1'S,1R,3S) ethyl [11-acetoxy-6-hydroxy-1-(2', 3', 6'-trideoxy-3'-trifluoroacetamido-4'-O-p-nitrobenzyl- L-lyxohexopyranose)-5,12-dioxo-3, 4, 5, 12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

26. The compound of claim 1 which is (1'S,1R,3S) or (1'S,1s,3R) Ethyl [11-hydroxy-1-(2', 3', 6'- trideoxy-3-trifluoroacetamido-L-lyxohexopyranose)- 5,12-dioxo-3, 4, 5, 12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

27. The compound of claim 1 which is (1'S,1R,3S) or (1'S,1S,3R) Ethyl [6-Methoxy, 11-hydroxy-1-(2', 3', 6'-trideoxy-3'- trifluoroacetamido-L-lyxohexopyranose)- 5,12-dioxo-3, 4, 5, 12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

28. The compound of claim 1 which is (1'S,1R,3S) or (1'S,1S,3R) Ethyl [11-Methoxy, 6-hydroxy-1-(2', 3', 6'-trideoxy-3'- trifluoroacetamido-L-lyxohexopyranose)- 5,12-dioxo-3, 4, 5, 12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

29. The compound of claim 1 which is (1'S,1R,3S) or (1'S,1S,3R) Ethyl [6-hydroxy-1-(2', 3', 6'- trideoxy-3'-trifluoroacetamido-L-lyxohexopyranose)- 5,12-dioxo-3, 4, 5, 12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

30. The compound of claim 1 which is (1'S,1R,3S) or (1'S,1S,3R) Methyl [6-hydroxy, 1-(2', 3', 6'- trideoxy-3'-trifluoroacetamido-L-lyxohexopyranose)- 5,12-dioxo-3, 4, 5, 12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

31. The compound of claim 1 which is P-nitrobenzyl [5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

32. The compound of claim 1 which is (1S, 3S) or (1R, 3R) P-nitrobenzyl [1-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

33. The compound of claim 1 which is (1'S,1R,3S) or (1'S,1S,3R) P-nitrobenzyl[-1-(2',3',6'-trideoxy-3'-trifluoroacetamido-4'-O-p-nitrobenzoyl-L-lyxohexopyranose)-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

34. The compound of claim 1 which is (1'S,1R,3S) or (1'S,1S,3R) methyl [1-(2', 3', 6'- trideoxy-3'-trifluoroacetamido-L-lyxohexopyranose)- 5,12-dioxo-3, 4, 5, 12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

35. The compound of claim 1 which is (1'S,1S,3S) or (1'S,1R,3R) methyl [1-(2', 3', 6'- trideoxy-3'-trifluoroacetamido-L-lyxohexopyranose)- 5,12-dioxo-3, 4, 5, 12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

36. The compound of claim 1 which is (1R, 3R) or (1S, 3S) cis-p-nitrobenzyl (5, 12-dioxo-1-methyl-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl) formate.

37. The compound of claim 1 which is (1S, 3R) or (1R, 3S) trans-p-nitrobenzyl (5, 12-dioxo-1-methyl-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl) formate.

38. The compound of claim 1 which is (1R, 3R) or (1S, 3S) cis-p-nitrobenzyl (5, 12-dioxo-7,10-dimethoxy-1-methyl-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl) formate.

39. The compound of claim 1 which is (1S, 3R) or (1R, 3S) trans-p-nitrobenzyl (5, 12-dioxo-7,10-dimethoxy-1-methyl-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl) formate.

40. The compound of claim 1 which is Methyl(11-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c]pyran-3-yl)ketone.

41. The compound of claim 1 which is Methyl(6-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c]pyran-3-yl)ketone.

42. The compound of claim 1 which is Methyl [6,11-diacetoxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] ketone.

43. The compound of claim 1 which is Methyl (6-hydroxy-11-acetoxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno-[2,3-c] pyran-3-yl) ketone.

44. The compound of claim 1 which is Methyl (11-hydroxy-6-acetoxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno-[2,3-c] pyran-3-yl) ketone.

45. The compound of claim 1 which is (1S,3S) or (1R,3R) Methyl [11-acetoxy-1,6-dihydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] ketone.

46. The compound of claim 1 which is (1'S,1S,3R) or (1'S,1R,3S) Methyl [11-acetoxy-6-hydroxy-1-(2', 3', 6'-trideoxy-3'-trifluoroacetamido-4'-O-p-nitrobenzoyl- L-lyxohexopyranose)-5,12-dioxo-3, 4, 5, 12-tetrahydroanthraceno [2,3-c] pyran-3-yl] ketone.

47. The compound of claim 1 which is (1'S,1S,3R) or (1'S,1R,3S) Methyl [11-acetoxy-6-hydroxy-1-(2', 3', 6'-trideoxy-3'-L-trifluoroacetamido- L-lyxonexopyranose)-5,12-dioxo-3, 4, 5, 12-tetrahydroanthraceno [2,3-c] pyran-3-yl] ketone.

48. The compound of claim 1 which is 3-(2-methoxymethoxy)aceto-6-hydroxy-1,2,3,4-tetrahydro-(2-oxygen)napthacene-5,12-dione.

49. The compound of claim 1 which is 3-(2-methoxymethoxy)aceto-11-hydroxy-1,2,3,4-tetrahydro-(2-oxygen)napthacene-5,12-dione.

50. The compound of claim 1 which is 3-(2-methoxymethoxy)aceto-6-acetoxy-1,2,3,4-tetrahydro-(2-oxygen)napthacene-5,12-dione.

51. The compound of claim 1 which is 3-(2-methoxymethoxy)aceto-11-acetoxy-1,2,3,4-tetrahydro-(2-oxygen)napthacene-5,12-dione.

52. The compound of claim 1 which is 3-(2-hydroxy-1-propyleneketal)aceto-6-acetoxy-1,2,3,4-tetrahydro-(2-oxygen)napthacene-5,12-dione.

53. The compound of claim 1 which is 3-(2-hydroxy-1-propyleneketal)aceto-11-acetoxy-1,2,3,4-tetrahydro-(2-oxygen)napthacene-5,12-dione.

54. The compound of claim 1 which is 3-(2-acetoxy-1-propyleneketal)aceto-6-acetoxy-1,2,3,4-tetrahydro-(2-oxygen)napthacene-5,12-dione.

55. The compound of claim 1 which is 3-(2-acetoxy-1-propyleneketal)aceto-11-acetoxy-1,2,3,4-tetrahydro-(2-oxygen)napthacene-5,12-dione.

56. The compound of claim 1 which is (1R,3R) or (1S,3S)-3-(2-acetoxy-1-propyleneketal)aceto-6-acetoxy-1-hydroxy-1,2,3,4-tetrahydro-(2-oxygen)napthacene-5,12-dione.

57. The compound of claim 1 which is (1R,3R) or (1S,3S)-3-(2-acetoxy-1-propyleneketal)aceto-11-acetoxy-1-hydroxy-1,2,3,4-tetrahydro-(2-oxygen)napthacene-5,12-dione.

58. The compound of claim 1 which is 3-(2-hydroxy)aceto-6-hydroxy-1,2,3,4-tetrahydro-(2-oxygen)napthacene-5,12-dione.

59. The compound of claim 1 which is 3-(2-hydroxy)aceto-11-hydroxy-1,2,3,4-tetrahydro-(2-oxygen)napthacene-5,12-dione.

60. The compound of claim 1 which is 6,11-diacetoxy-3-(2-methoxymethoxy)aceto-1,2,3,4-tetrahydro-(2-oxygen)naphthacene-5,12-dione.

61. The compound of claim 1 which is (1R,3R) or (1S,3S)-3-(2-hydroxy)aceto-6-acetoxy-1-hydroxy-1,2,3,4-tetrahydro-(2-oxygen)napthacene-5,12-dione.

62. The compound of claim 1 which is (1R,3R) or (1S,3S)-3-(2-hydroxy)aceto-11-acetoxy-1-hydroxy-1,2,3,4-tetrahydro-(2-oxygen)napthacene-5,12-dione.

63. The compound of claim 1 which is 3-carbomethoxy-6-hydroxy-1,2,3,4-tetrahydro-(2-sulfur)naphthacene-5,12-dione.

64. The compound of claim 1 which is 3-carbomethoxy-11-hydroxy-1,2,3,4-tetrahydro-(2-sulfur)naphthacene-5,12-dione.

65. The compound of claim 1 which is 3-carbomethoxy-6-acetoxy-1,2,3,4-tetrahydro-(2-sulfur)naphthacene-5,12-dione.

66. The compound of claim 1 which is 3-carbomethoxy-11-acetoxy-1,2,3,4-tetrahydro-(2-sulfur)naphthacene-5,12-dione.

67. The compound of claim 1 which is (1S,3S) or (1R,3R)-Methyl(1-methoxy-6-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl)ketone.

68. The compound of claim 1 which is (1S,3S) or (1R,3R)-Methyl(1-methoxy-11-hydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl)ketone.

69. The compound of claim 1 which is (1S,3S) or (1R,3R)-Methyl(1,6-dihydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl)ketone.

70. The compound of claim 1 which is (1S,3S) or (1R,3R)-Methyl(1,11-dihydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl)ketone.

71. The compound of claim 1 which is (1S,3S) or (1R,3R)-6-hydroxy-1-methoxy-1,2,3,4-tetrahydro-3-vinyl-(2-oxygen)naphthacene-5,12-dione.

72. The compound of claim 1 which is (1S,3S) or (1R,3R)-6-acetoxy-1-methoxy-1,2,3,4-tetrahydro-3-vinyl-(2-oxygen)naphthacene-5,12-dione.

73. The compound of claim 1 which is (1S,3S) or (1R,3R)-6-acetoxy-1-hydroxy-1,2,3,4-tetrahydro-3-vinyl-(2-oxygen)naphthacene-5,12-dione.

74. The compound of claim 1 which is (1S,3S) or (1R,3R)-Methyl [1,11-dihydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

75. The compound of claim 1 which is (1S,3S) or (1R,3R)-Methyl [1,6-dihydroxy-5,12-dioxo-3,4,5,12-tetrahydroanthraceno [2,3-c] pyran-3-yl] formate.

76. The compound of claim 1 which is 5,12-dimethoxy-3-carbomethoxy-1,2,3,4-tetrahydro-[illegible]
dione

77. The compound of claim 1 which is 5,12-dihydroxy-3-carbomethoxy-1,2,3,4-tetrahydro-(2-sulfur)-napthacene-6,11-dione.

78. The compound which is Ethyl (7-chloro-5,8-dioxo-5,8-dihydroisochroman-3-yl) formate.

79. The compound which is Methyl (5,8- dioxo-5,8-dihydroisochroman-3-yl) formate.

80. The compound which is p-Nitrobenzyl (5,8 dioxo-5,8-dihydroisochroman-3-yl) formate.

81. The compound which is cis-p-Nitrobenzyl (5,8-dioxo-1-methyl-5,8-dihydroisochroman-3-yl) formate.

82. The compound which is trans-p-Nitrobenzyl (5,8-dioxo-1-methyl-5,8-dihydroisochroman-3-yl) formate.

83. The compound which is Methyl (5,8-dioxo-5,8-dihydroisochroman-3-yl) ketone.

84. The compound which is 5,8-dimethoxy-3-(methoxymethoxy) acetoisochroman.

85. The compound which is 3-(methoxymethoxy) aceto-5,8-dioxoisochroman.

86. The compound which is 3-carbomethoxy-5,8-dimethoxyisothiochroman.

87. The compound which is 3-carbomethoxy-5,8-dioxoisothiochroman.

88. The compound which is Methyl(1,5,8-trimethoxyisochroman-3-yl) ketone dimethoxy ketal.

89. The compound which is Methyl (1-methoxy-5,8-dioxo-5,8-dihydroisochroman-3-yl) ketone.

90. The compound which is Methyl(5,8 dimethoxy-1-hydroxyisochroman-3-yl) ketone.

91. The compound which is Methyl (1-hydroxy-5,8-dioxo-5,8-dihydroisochroman-3-yl) ketone.

92. The compound which is 1-methoxy-3-vinylisochroman-5,8 dione.

93. The compound which is Methyl(5,8-dimethoxy-1-hydroxyisochroman-3-yl) formate.

94. The compound which is Methyl (1,5,8-trimethoxyisochroman-3-yl) formate.

95. The compound which is Methyl(1-methoxy-5,8-dioxo-5,8-dihydroisochroman-3-yl) formate.

96. The compound which is 1-hydroxy-5,8-dioxo-3-methyl-5,8-dihydroisochroman.

97. The compound which is 1,4-dihydroxy-3-hydroxymethyl-5,8-dioxo-5,8-dihydroisochroman.

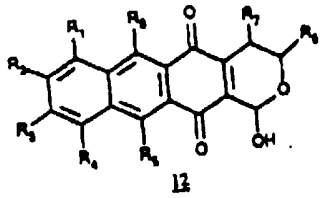
98. The compound which is Methyl (1-hydroxy-5,8-dioxo-5,8-dihydroisochroman-3-yl) formate.

99. The compound of claim 1 which is 5,8-dimethoxyisochroman-3-yl formic acid.

100. The compound which is 3-carbmethoxy-5,8-dimethoxy-isothiochroman.

101. The compound which is 1-hydroxy-3-(ethane-1-onedioxane ketal-5,8-dioxo-5,8-dihydroisochroman.

102. A compound of the formula:



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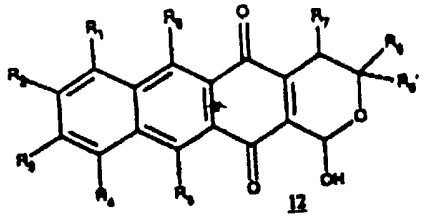
wherein R_1 through R_8 are as defined in claim 1.

103. A compound of the formula:



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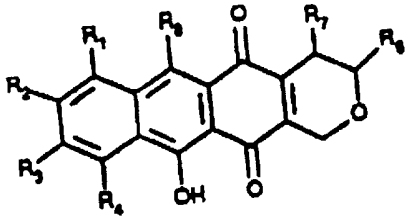
wherein R_1 through R_8 are as defined in claim 1.

104. A compound of the formula:



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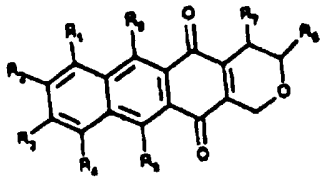
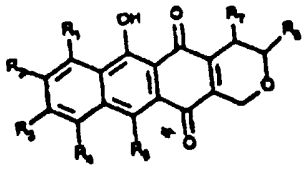
wherein R_1 through R_4 and R_6 through R_8 are as defined in claim 1.

105. A compound of the formula:



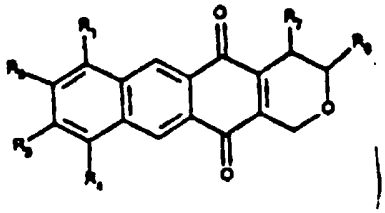
wherein R_1 through R_8 are as defined in claim 1.

106. A compound of the formula:



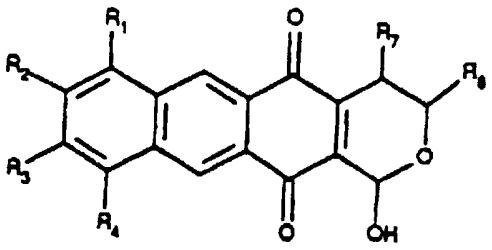
wherein R_1 through R_7 are as defined in claim 1.

107. A compound of the formula:



wherein R_1 through R_4, R_6 and R_7 are as defined in claim 1.

108. A compound of the formula:



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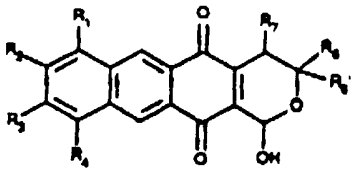
wherein R_1 through R_4, R_6 and R_7 are as defined is claim 1.

109. A compound of the formula:



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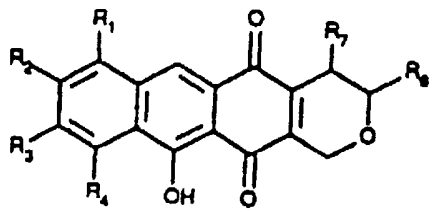
wherein R_1 through R_4, R_6, R_6' and R_7 are as defined in claim 1.

110. A compound of the formula:



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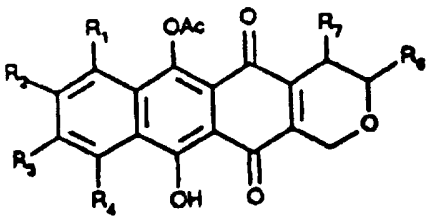
wherein R_1 through R_4, R_6 and R_7 are as defined in claim 1.

111. A compound of the formula:



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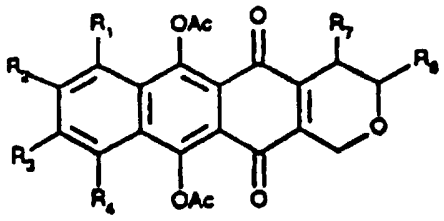
wherein R_1 through R_4, R_6 and R_7 are as defined in claim 1.

112. A compound of the formula:



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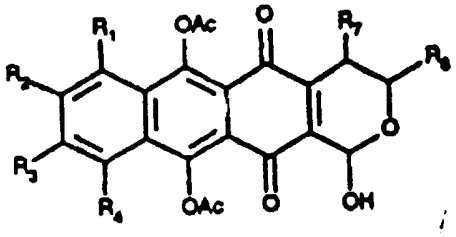
wherein R_1 through R_4, R_6 and R_7 are as defined in claim 1.

113. A compound of the formula:



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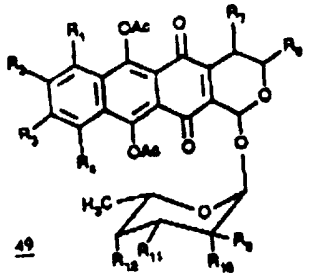
wherein R_1 through R_4, R_6 and R_7 are as defined in claim 1.

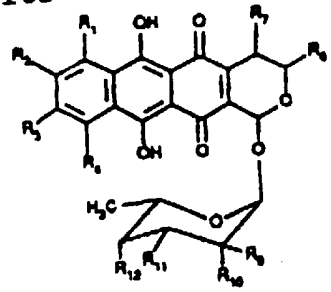
114. A compound of the formula:



49

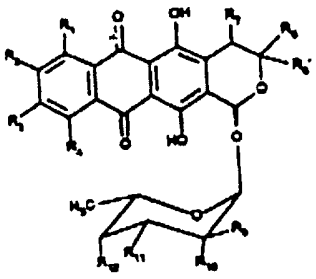
wherein R_1 through R_4, R_6 and R_7 and R_9 through R_{12} are as defined in claim 1.

115. A compound or its tautomer of the formula:



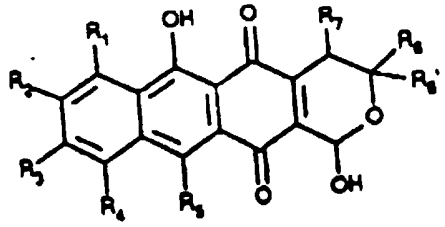
wherein R_1 through R_4, R_6 and R_7 and R_9 through R_{12} are as defined in claim 1.

116. A compound or its tautomer of the formula:



wherein R_1 through R_4 and R_6, R_6', R_7 and R_9 through R_{12} are as defined in claim 1.

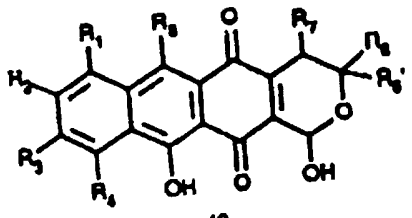
117. A compound of the formula:



39

wherein R_1 through R_7 are as defined in claim 1.

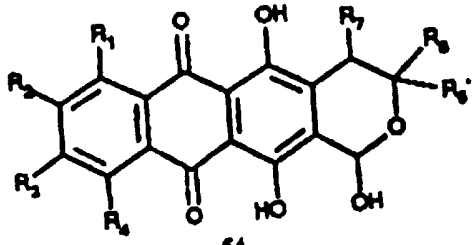
118. A compound of the formula:



40

wherein R_1 through R_4 and R_6 through R_8 are as defined in claim 1.

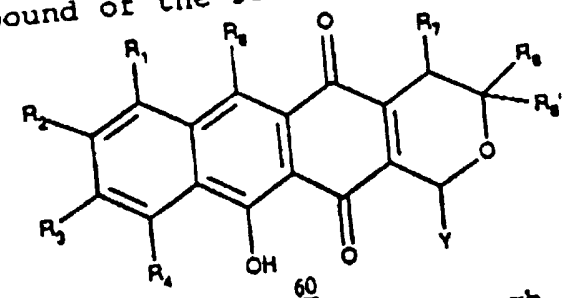
119. A compound or its tautomer of the formula:



54

wherein R_1 through R_4 and R_6, R_6' and R_7 are as defined in claim 1.

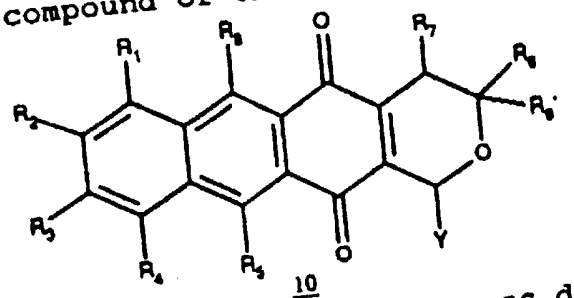
120. A compound of the formula:



60

wherein R_1 through R_4 and R_6 through R_8 and Y are as defined in claim 1.

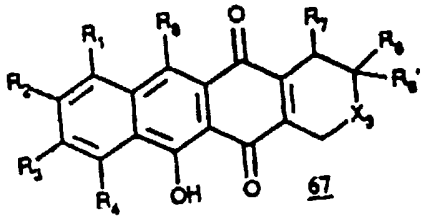
121. A compound of the formula:



10

wherein R_1 through R_8 and Y are as defined in claim 1.

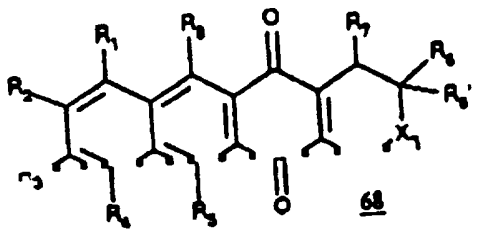
122. A compound of the formula:



67

wherein R_1 through R_4, R_6 through R_8 and X_3 are as defined in claim 1.

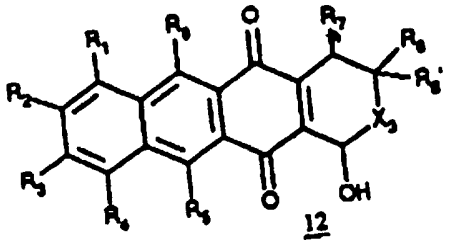
123. A compound of the formula:



68

wherein R_1 through R_8 and X_3 are as defined in claim 1.

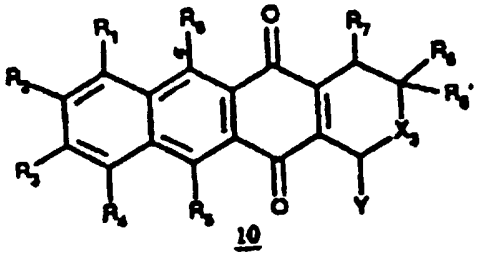
124. A compound of the formula:



12

wherein R_1 through R_8, and X_3 are as defined in claim 1.

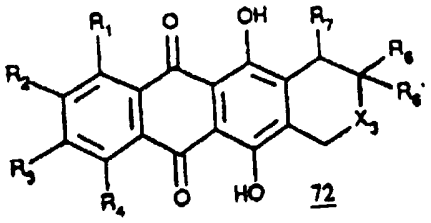
125. A compound of the formula:



10

wherein R_1 through R_8, X_3 and Y are as defined in claim 1.

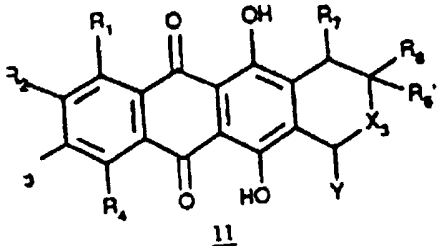
126. A compound and its tautomer of the formula:



72

wherein R_1 through R_4, R_6, R_6', R_7 and X_3 are as defined in claim 1.

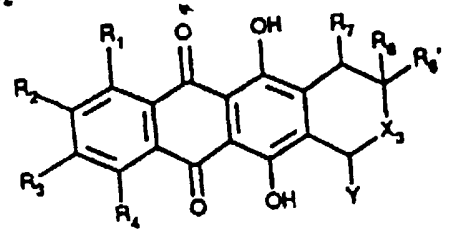
127. A compound and its tautomer of the formula:



11

wherein R_1 through R_4, R_6, R_6', R_7 and X_3 and Y are as defined in claim 1.

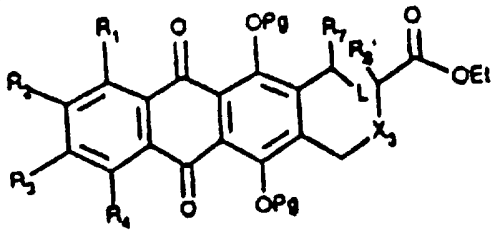
128. A compound of the formula:



11

wherein R_1 through R_4, R_6, R_6', R_7 and X_3 are as defined in claim 1, Pg is a protecting group and L is a leaving group.

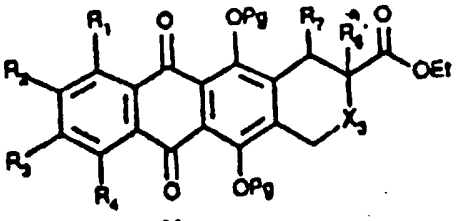
129. A compound of the formula:



92

wherein R_1 through R_4, R_6', R_7 and X_3 are as defined in claim 1 and Pg is a protecting group.

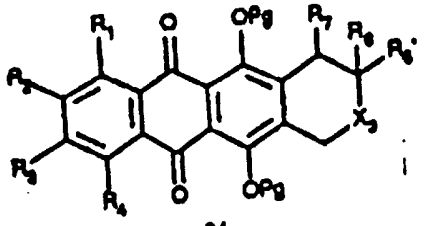
130. A compound of the formula:



93

wherein R_1 through R_4, R_6', R_7 and X_3 are as defined in claim 1 and wherein Pg is a protecting group.

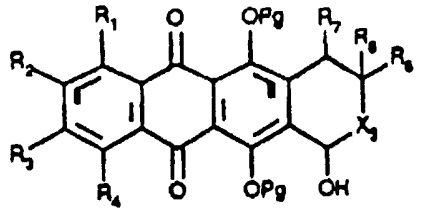
131. A compound of the formula:



94

wherein R_1 through R_4, R_6, R_6', R_7 and X_3 are as defined in claim 1 and Pg is a protecting group.

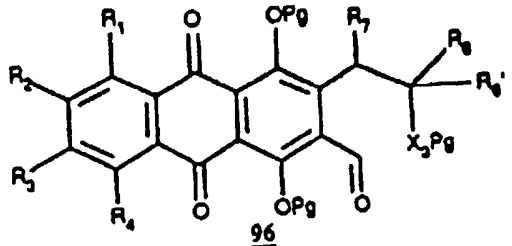
132. A compound of the formula:



95

wherein R_1 through R_4, R_6, R_6', R_7 and X_3 are as defined in claim 1 and Pg is a protecting group.

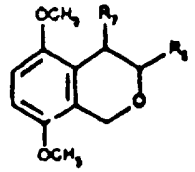
133. A compound of the formula:



96

wherein R_1 through R_4, R_6, R_6', R_7 and X_3 are as defined in claim 1, Pg is a protecting group and L is a leaving group.

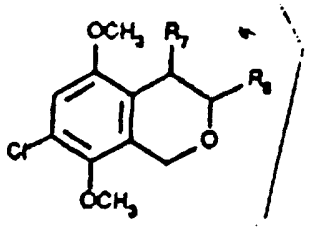
134. A compound of the formula:



20

wherein R_6 and R_7 are as defined in claim 1.

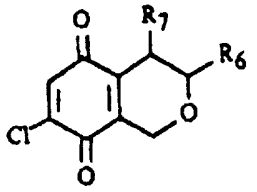
135. A compound of the formula:



21

wherein R_6 and R_7 are as defined in claim 1.

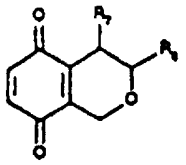
136. A compound of the formula:



22

wherein R_6 and R_7 are as defined in claim 1.

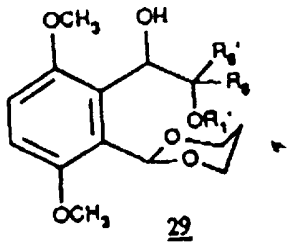
137. A compound of the formula:



26

wherein R_6 and R_7 are as defined in claim 1.

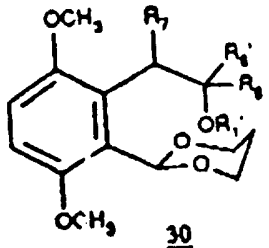
138. A compound of the formula:



29

wherein R_6 and R_6' are as defined in claim 1, and R_1 is a protecting group.

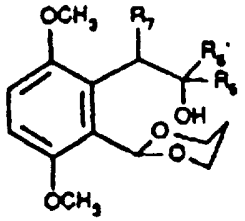
149. A compound of the formula:



30

wherein R_6, R_6' and R_7 are as defined in claim 1 and R_1 is a protecting group.

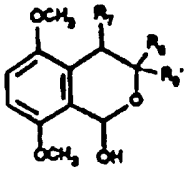
140. A compound of the formula:



32

wherein R_6, R_6' and R_7 are as defined in claim 1.

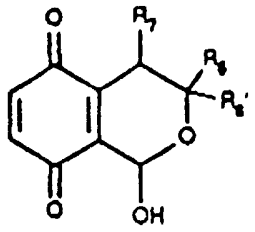
141. A compound of the formula:



33

wherein R_6, R_6' and R_7 are as defined in claim 1.

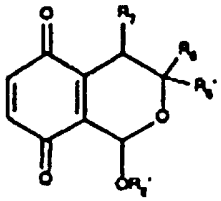
142. A compound of the formula:



34

wherein R_6, R_6' and R_7 are as defined in claim 1.

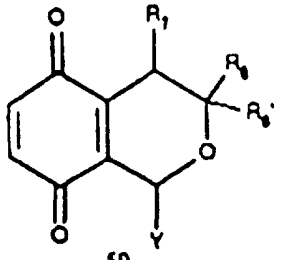
143. A compound of the formula:



35

wherein R_6, R_6' and R_7 are as defined in claim 1 and R_2' is a protecting group.

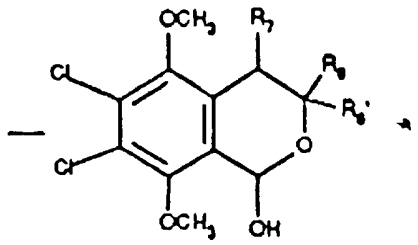
144. A compound of the formula:



59

wherein R_6, R_6', R_7 and Y are as defined in claim 1.

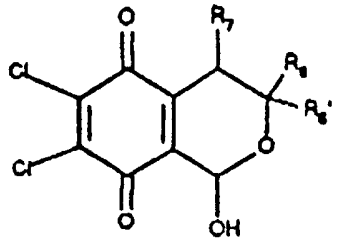
145. A compound of the formula:



36

wherein R_6, $R_6'$and R_7 are as defined in claim 1.

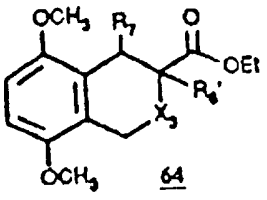
146. A compound of the formula:



37

wherein R_6, $R_6'$and R_7 are as defined in claim 1.

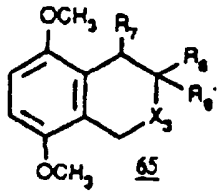
157. A compound of the formula:



64

wherein R_6', R_7 and X_3 are as defined in claim 1.

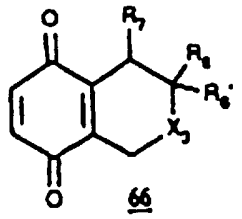
148. A compound of the formula:



65

wherein R_6, R_6', R_7 and X_3 are as defined in claim 1.

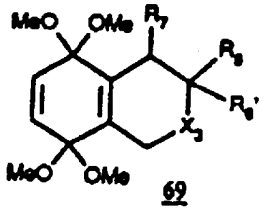
149. A compound of the formula:



66

wherein R_6, R_6', R_7 and X_3 are as defined in claim 1.

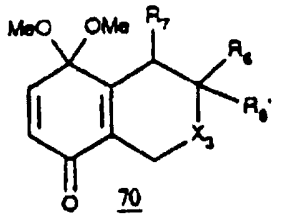
150. A compound of the formula:



69

wherein R_6, R_6', R_7 and X_3 are as defined in claim 1.

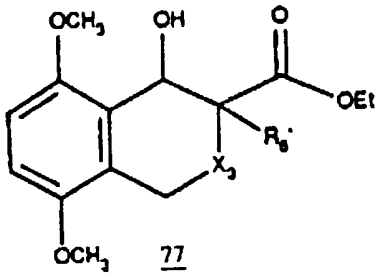
151. A compound of the formula:



70

wherein R_6, R_6', R_7 and X_3 are as defined in claim 1.

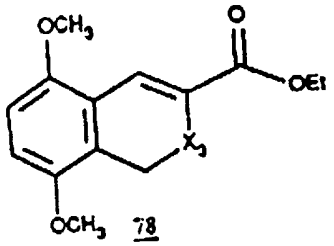
152. A compound of the formula:



77

wherein R_6' and X_3 are as defined in claim 1.

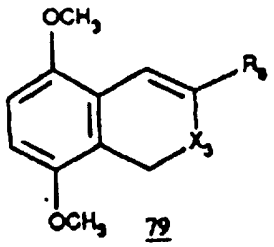
153. A compound of the formula:



78

wherein X_3 is as defined in claim 1.

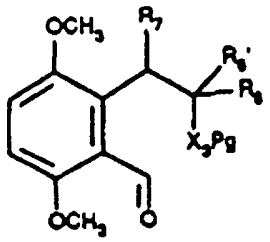
154. A compound of the formula:



79

wherein R_6 and X_3 are as defined in claim 1.

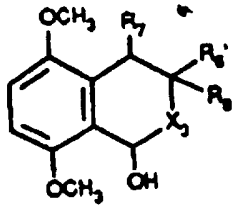
155. A compound of the formula:



83

wherein R_6, R_6', R_7 and X_3 are as defined in claim 1 and Pg is a protecting group.

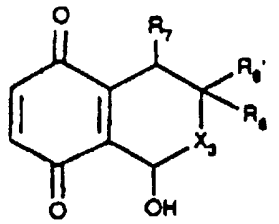
156. A compound of the formula:



84

wherein R_6, R_6', R_7 and X_3 are as defined in claim 1.

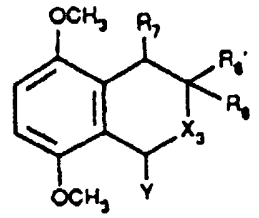
157. A compound of the formula:



85

wherein R_6, R_6', R_7 and X_3 are as defined in claim 1.

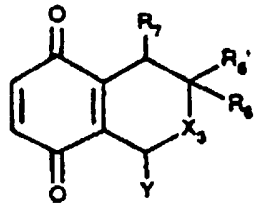
158. A compound of the formula:



86

wherein R_6, R_6', R_7, X_3 and Y are as defined in claim 1.

159. A compound of the formula:



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wherein R_6, R_6', R_7, X_3 and Y are as defined in claim 1.

160. A pharmaceutical composition possessing antitumor or anticancer activity, comprising an effective amount of at least one compound according to claim 1 and a pharmaceutically acceptable carrier.

161. A pharmaceutical composition possessing antitumor or anticancer activity, comprising an effective amount of at least one compound according to claim 2 and a pharmaceutically acceptable carrier.

162. A pharmaceutical composition possessing antitumor or anticancer activity, comprising an effective amount of at least one compound according to claim 3 and a pharmaceutically acceptable carrier.

163. A pharmaceutical composition possessing antitumor or anticancer activity, comprising an effective amount of at least one compound according to claim 4 and a pharmaceutically acceptable carrier.

164. A pharmaceutical composition according to any one of claims 160 through 163, and further comprising an effective amount of at least one therapeutic agent.

165. A pharmaceutical composition according to any one of claims 160 through 163 wherein said compound is bound to an agent facilitating targeting of said compound to tumor or cancer cells.

166. A pharmaceutical composition according to claim 164 wherein said agent is selected from monoclonal antibodies, polyclonal antibodies,

proteins and liposomes.

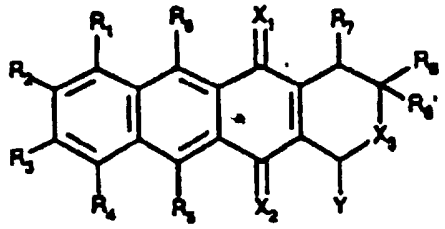
167. A pharmaceutical composition possessing antitumor or anticancer activity, comprising at least one compound as claimed in any one of claims 102 through 159, and a pharmaceutically acceptable carrier.

168. A pharmaceutical composition according to claim 167 and further comprising an effective amount of at least one therapeutic agent.

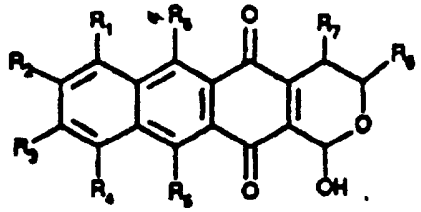
169. A pharmaceutical composition according to claim 167, wherein said compound is bound to an agent facilitating targeting of said compound to tumor or cancer cells.

170. A pharmaceutical composition according to claim 167, wherein said agent is selected from monoclonal antibodies, polyclonal antibodies, proteins and liposomes.

171. A process for preparing a compound of the formula:



wherein R_1 through R_8 and X_1, X_2, X_3 are as defined in claim 1 and Y is a saccharide as defined in claim 1, said process comprising the step of reacting a compound of the formula (12):



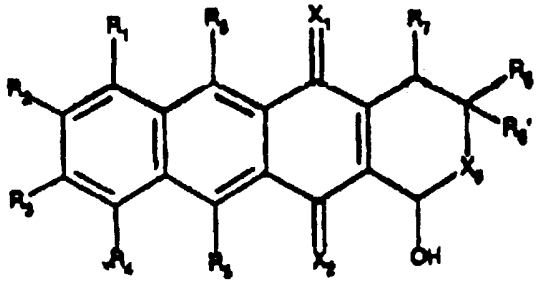
12

wherein R_1 through R_8, X_1, X_2 and X_3 are as defined above, with a compound of the formula (13):

13

wherein R_9 through R_{12} are as defined above and L is a displaceable atom or group.

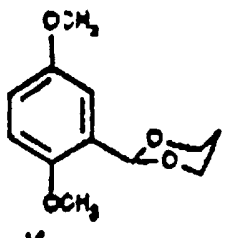
172. A process for preparing a compound of the formula:



12

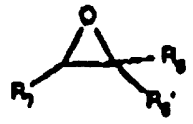
wherein R_1 through R_8 are as defined in claim 1 and X_1, X_2 and X_3 are oxygen, said process comprising the steps of:

reacting a lithio salt of an acetal of the formula (15):

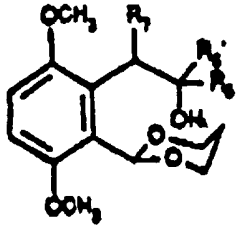


15

with an epoxide of the formula (31)

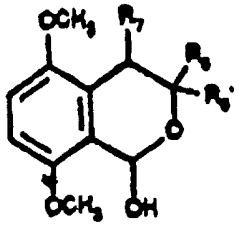


optionally in the presence of a Lewis acid to form a compound of formula (32)



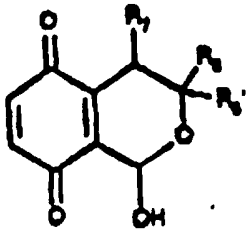
32

cyclizing the compound of formula (32) to give the compound of formula (33)



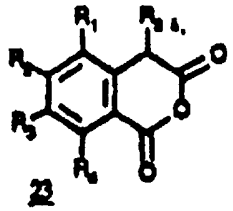
33

oxidizing the compound of formula (33) to give a compound of formula (34)



34

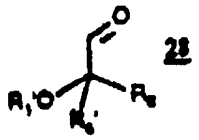
converting the compound of formula (34) to compounds of formula (39) and (40) by reacting with a compound of the formula (23)



23

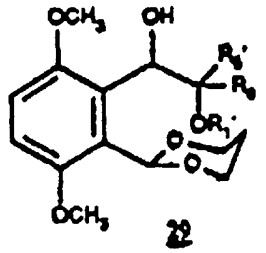
and converting the compounds of (39) and (40) to a compound of the formula (12).

173. A process according to claim 172, wherein said compound of formula (32) is obtained by reacting said compound of formula (15) with a compound of the formula (28)



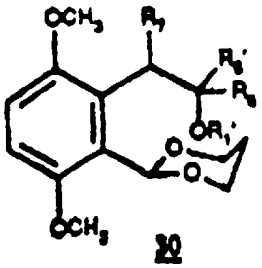
28

wherein R'_1 is a protecting group and R_6 and R'_6 are as defined in claim 1, to form a compound of the formula (29)



29

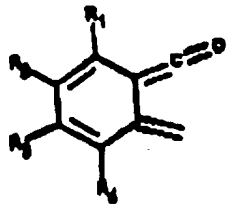
reacting said compound of formula (29) with a compound of the formula R_7CH_2X wherein X is halogen and R_7 is as defined in claim 1 to form a compound of the formula (30)



30

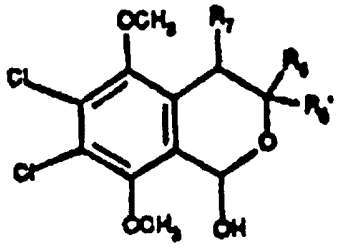
and deprotecting said compound of the formula (30) to form said compound of formula (32).

174. A process according to claim 172, wherein instead of compound (23) there is used a compound of the formula (23')



23'

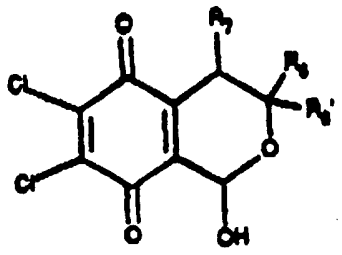
175. A process according to claim 172, wherein said compound (33), instead of being oxidized to the compound of formula (34), is reacted to form a compound of the formula (36)



36

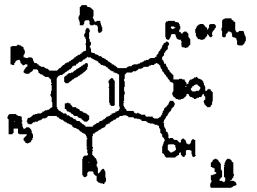
which is then reacted to form a compound of the

formula (37)



37

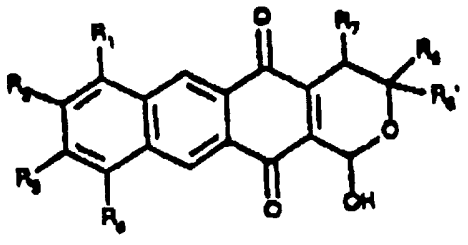
and said compound of formula (37) is reacted with a compound of the formula (38)



38

to form said compounds of formula (39) and (40).

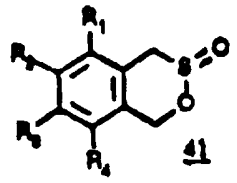
176. A process for preparing a compound of the formula (44),



44

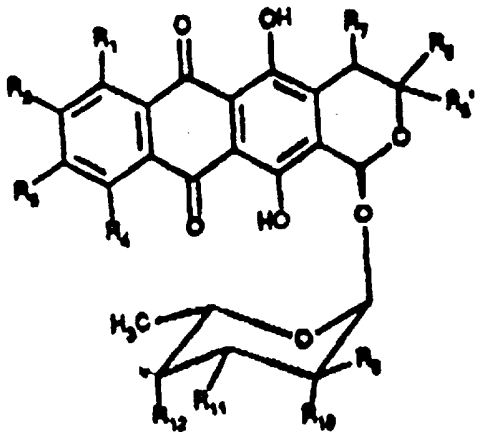
wherein R_1 to R_4, R'_6, R_6 and R_7 are as defined in claim 1, said process comprising the step of reacting a compound of the formula (34), as defined in claim 172, with an o-quinodimethane

obtained by thermolysis of a compound of the formula (41)



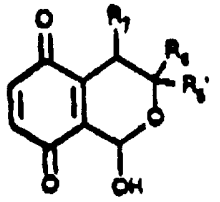
41

177 A process for preparing a compound of the formula (11),



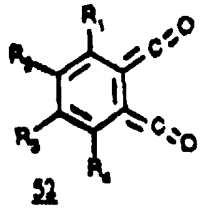
11 (X_3=O, Y=Saccharide)

wherein R_1 through R_4, R_6, R'_6, and R_7 are as defined in claim 1, which process comprises the steps of reacting a compound of the formula (34)



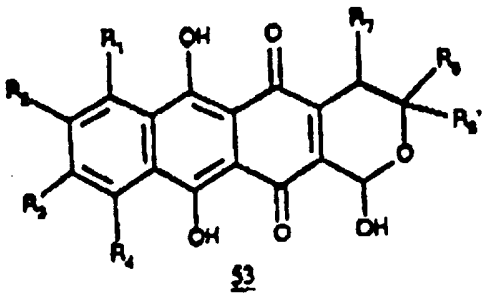
24

as defined in claim 172 with a compound of the formula (52)

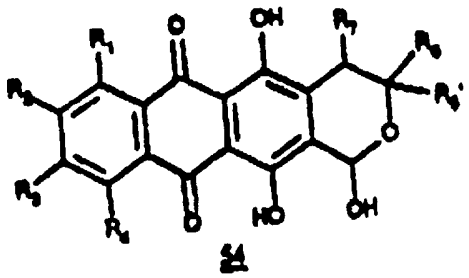


52

wherein R_1 through R_4 are as defined in claim 1, under U.V. irradiation to give a tautomeric mixture of compounds of the formula (53) and (54),



53

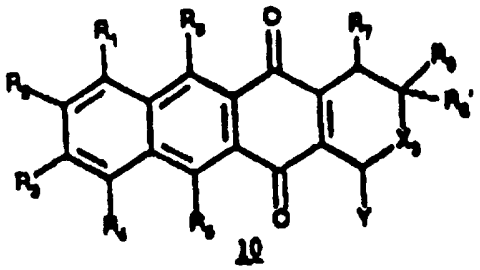


54

and glycosiding said tautomeric compound mixture of (53) and (54) to give the compound of formula (11).

178. A process for preparing a compound of the

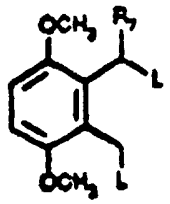
formula:



10

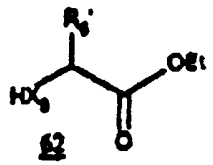
wherein R_1 through R_8, X_3 and Y are as defined in claim 1, said process comprising the steps of:

reacting an intermediate of formula (61):



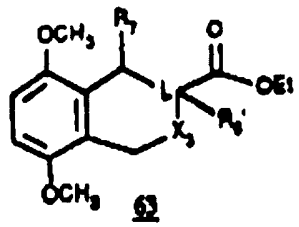
61

wherein L is a displaceable atom or group, with a compound of formula (62):



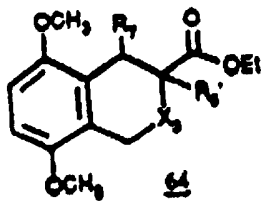
62

in the presence of base to give an adduct of formula (63):



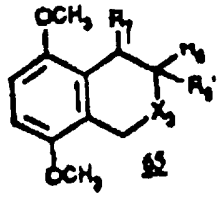
63

cyclizing the compound of formula (63) in the presence of base, to give the intermediate of formula (64):



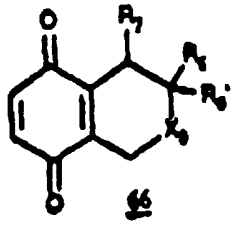
64

converting the compound of formula (64) into a compound of formula (65):

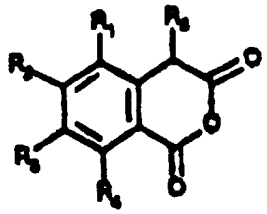


65

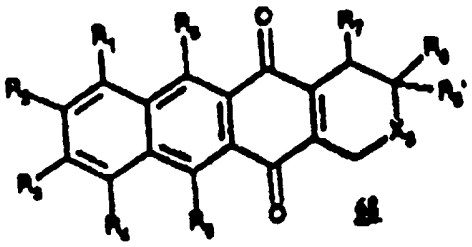
oxidizing the compound of formula (65) to give a compound of the formula (66):



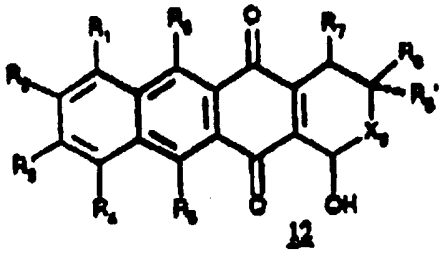
converting the compound of formula (66) to a compound of formula (67) by reacting with a compound of the formula (23):



and converting the compound of formula (67) to a compound of formula (68):



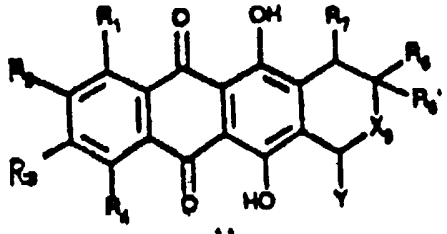
oxidizing the compound of formula (68) to give a compound of formula (12)



12

and converting the compound of formula (12) to a compound of formula (10).

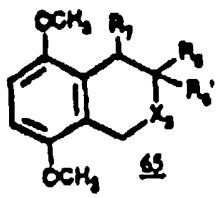
179. A process for preparing a compound of the formula (11):



11

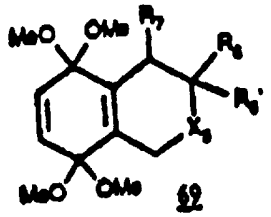
wherein R_1 through R_7, R'_6, X_3 and Y are as defined in claim 1, said process comprising the steps of:

electrochemically reducing in the presence of base, a compound of formula (65):



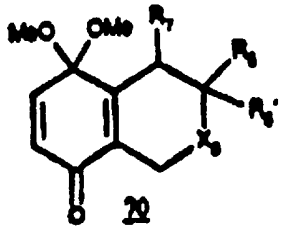
65

to give a compound of formula (69):



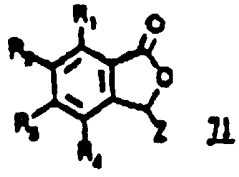
69

partially hydrolysing the compound of formula (69) under acidic conditions to give a compound of formula (70):



70

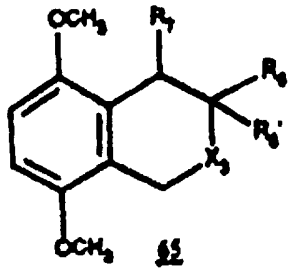
converting the compound of formula (70) into a compound of formula (72) by reacting with a compound of formula (71):



71

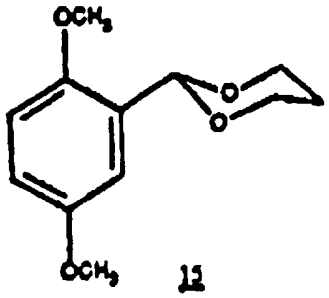
wherein Z is an electron withdrawing group, and converting the compound of formula (72) to a compound of formula (11).

180. A process for preparing a compound of the formula (65):

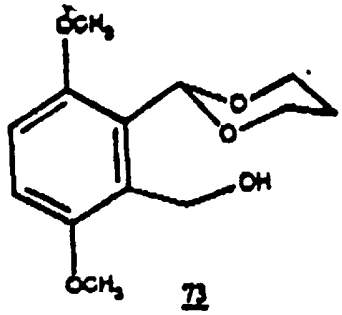


wherein R_6, R'_6 and R_7 are as defined in claim 1, said process comprising the steps of:

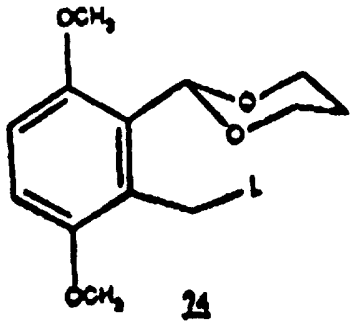
reacting a lithio salt of an acetal of the formula (15):



with formaldehyde to give an adduct of formula (73)

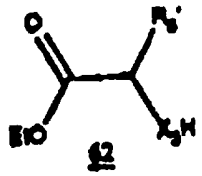


converting a compound of formula (73) to an intermediate of formula (74):



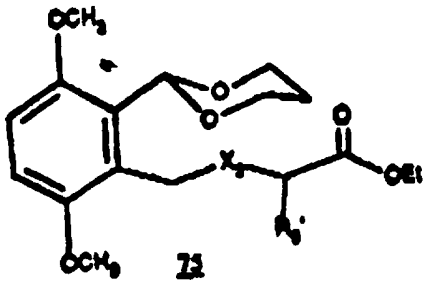
74

wherein L is a displaceable atom or group, reacting the compound of formula (74), in the presence of a base, with a compound of formula (62):



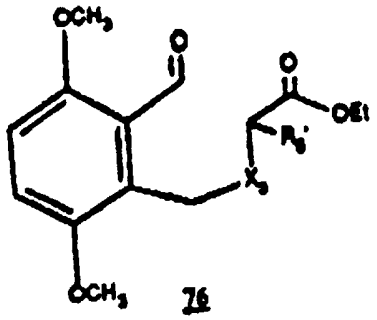
62

to give an adduct of formula (75):



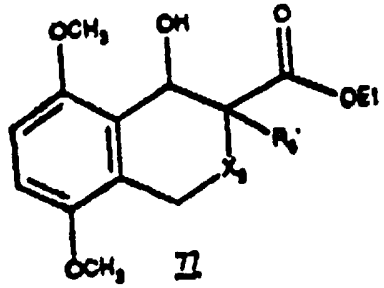
75

hydrolysing under acidic conditions a compound of formula (75) to give a benzaldehyde of formula (76):



76

cyclizing the compound of formula (76) under basic conditions to give the compound of formula (77):

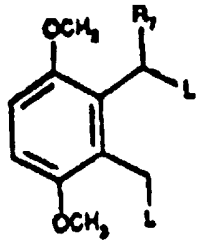


77

and converting the compound of formula (77) to the compound of formula (65).

181. A process for preparing a compound of formula (65) as defined in claim 180, said process comprising the steps of:

reacting, in the presence of base, a compound of formula (61):

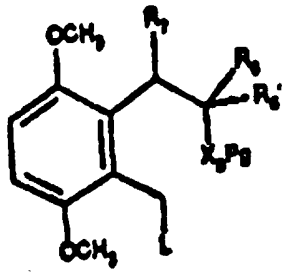


61

wherein L is a displaceable atom or group, with a compound of fomula (80):

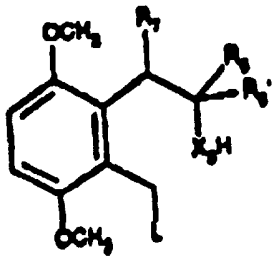
80

wherein R_6 and/or R'_6 are preferably electron withdrawing groups and Pg is a protecting group, to give an adduct of formula (8.):



81

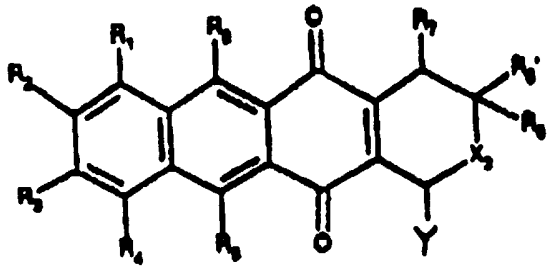
deprotecting the compound of formula (81) to give a compound of formula (82):



82

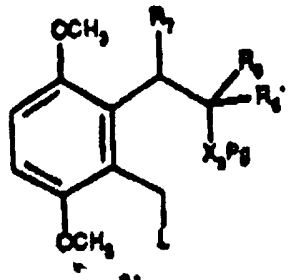
and cyclizing the compound of formula (82), under basic conditions, to give the compound of formula (65).

182 . A process for preparing a compound of formula (10):



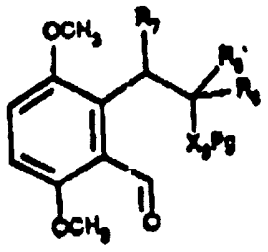
wherein R_1 through R_8, R'_6, Y and X_3 are as defined in claim 1, said process comprising the steps of:

oxidizing a compound of formula (81):



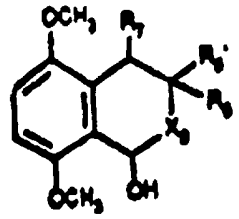
81

wherein Pg is a protecting group, to give a compound of formula (83):



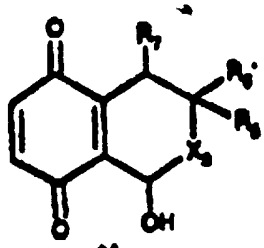
82

deprotecting and cyclizing, under basic conditions, the compound of formula (83) to give the intermediate of formula (84):



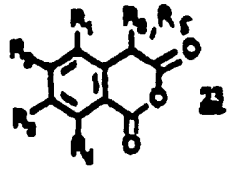
84

oxidizing the compound of formula (84) to give a compound of formula (85):



85

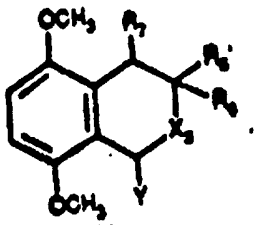
converting the compound of formula (85) to the compound of formula (12) by reacting with a compound of formula (23):



23

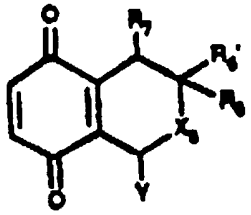
and converting the compound of formula (12) to the compound of formula (10).

183. A process according to claim 182, wherein said compound of formula (10) is obtained by converting the compound of formula (84) to the compound of formula (86):



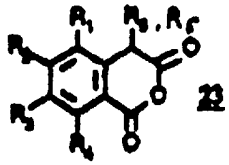
86

oxidizing the compound of formula (86) to give a compound of formula (87):



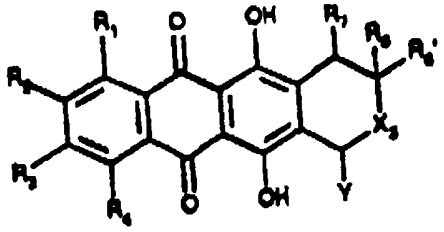
87

and reacting the compound of formula (87) with a compound of formula (23):



22

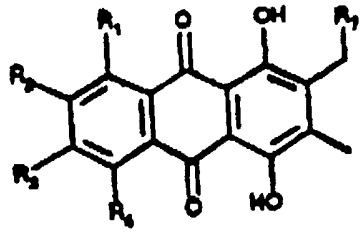
184 . A process for preparing a compound of the formula (11):



11

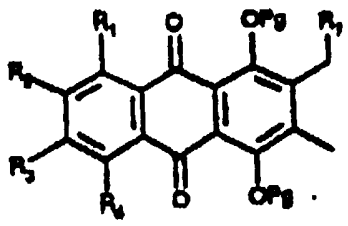
wherein R_1 through R_8, R_6, X_3, and Y are as defined in claim 1, said process comprising the steps of:

protecting the compound of formula (88):



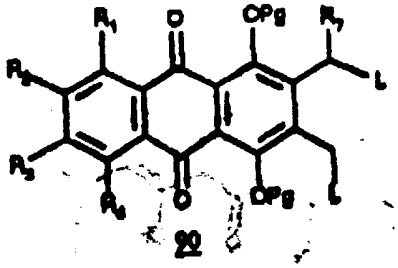
11

to give a compound of formula (89):



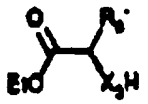
12

wherein Pg is a protecting group, converting the compound of formula (89) to a compound of formula (90):



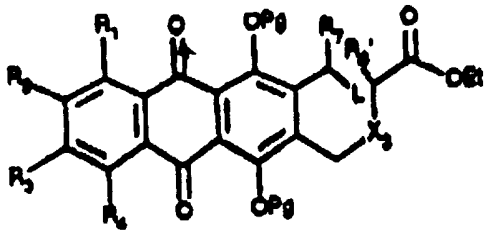
90

wherein L is a displaceable atom or group, reacting the compound of formula (90), under basic conditions, with a compound of formula (62):



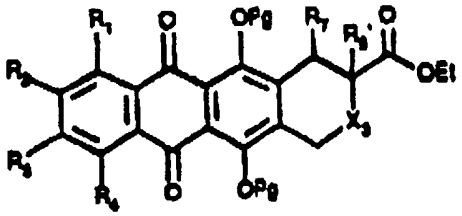
62

to give a compound of formula (92):



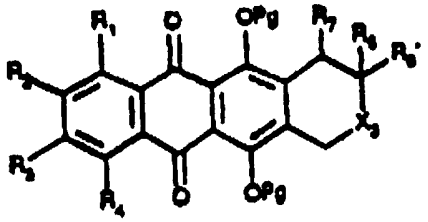
92

cyclizing the compound of formula (92) to the compound of formula (93):



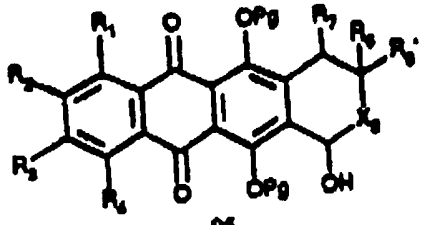
92

converting the compound of formula (92) to the compound of formula (94):



94

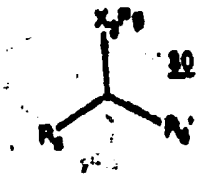
oxidizing the compound of formula (94) to give the compound of formula (95):



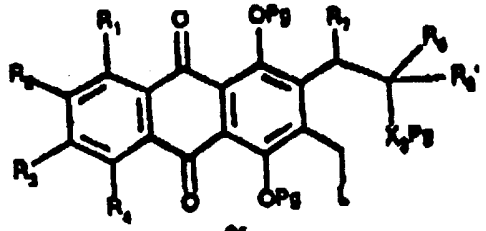
95

and converting the compound of formula (95) to the compound of formula (11).

185 . A process according to claim 184, wherein said compound of formula (11) is obtained by reacting said compound of formula (90) with a compound of formula (80):



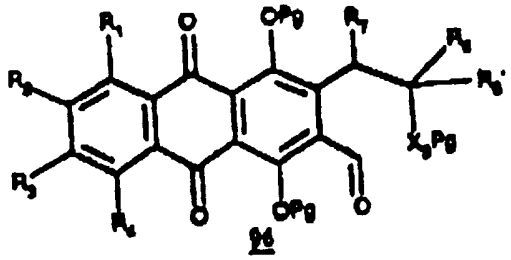
wherein R_6 and/or R'_6 are electron withdrawing, to give an adduct of formula (91):



and cyclizing to a compound of formula (93) which is then converted to the compound of formula (11).

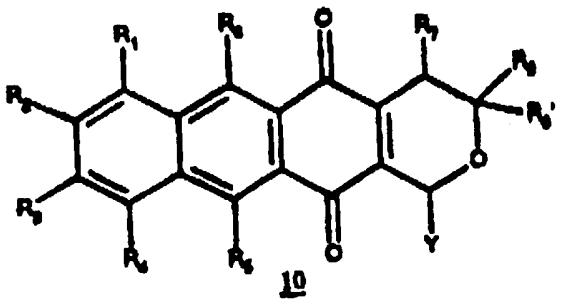
185

186 . A process according to claim , wherein said compound of formula (11) is obtained by oxidizing said compound of formula (91) to give the intermediate of formula (96):



and deprotecting and cyclizing the compound of formula (96) to give the compound of (95) which is then converted to the compound of formula (11).

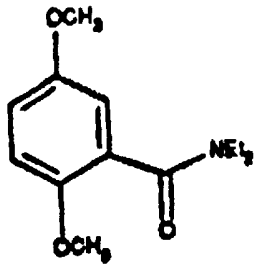
187. A process for the preparation of compound of formula



10

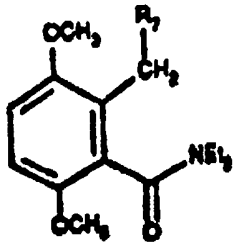
wherein R_1 to R_5, R'_6, R_6 to R_8 and Y are as defined in claim 1, said process comprising the steps of:

treating 2,5-dimethoxybenzoic acid with oxalyl chloride in the presence of a base, and then with diethylamine to give a benzamide of formula (55a):



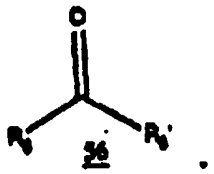
55a

treating the compound of formula (55a) with a strong base in a solvent to give a lithio salt, which is then reacted with an electrophile, $L\text{-}CH_2\ R_7$, wherein R_7 is as defined in claim 191 and L is a displaceable atom or group, to give a benzo derivative of formula (55b):



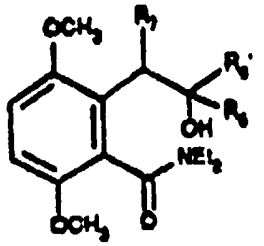
55b

reacting the benzo derivative of formula (55b) with an electrophile of formula (56),



56

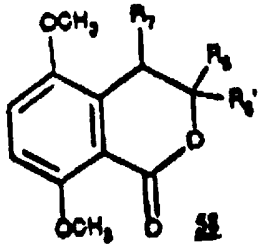
wherein R_6 and R'_6 are as defined above, in the presence of a strong base in a solvent to give an adduct of formula (57),



57

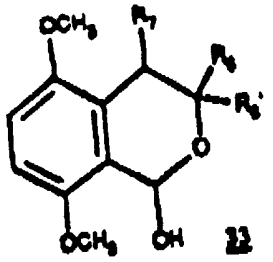
wherein R_6, R'_6 and R_7 are as defined above;

cyclizing the adduct of formula (57) in the presence of an acid to an isochromanone of formula (58),



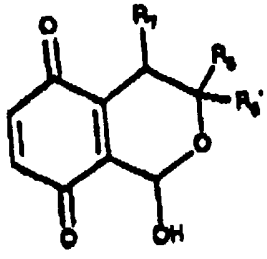
58

wherein R_6, R'_6 and R_7 are as defined above,
reducing the compound of formula (58) with an hydride to the hydroxyisochroman of formula (33).



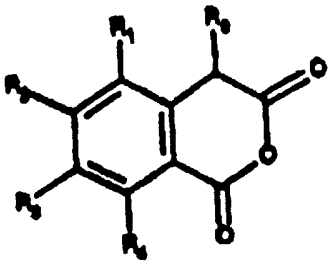
33

wherein R_6, R'_6 and R_7 are as defined above,
oxidatively demethylating the compound of formula (33) with ceric ammonium nitrite to give an isochromandione of formula (34).



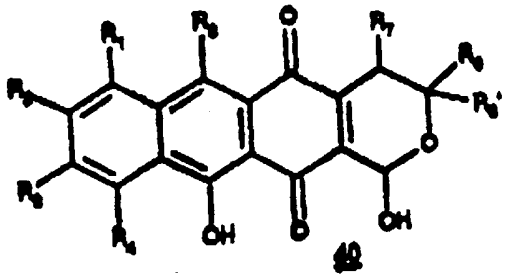
34

wherein R_6, R'_6 and R_7 are as defined above;
optionally coupling the compound of formula 34 with an homophthalic anhydride of formula (23)



21

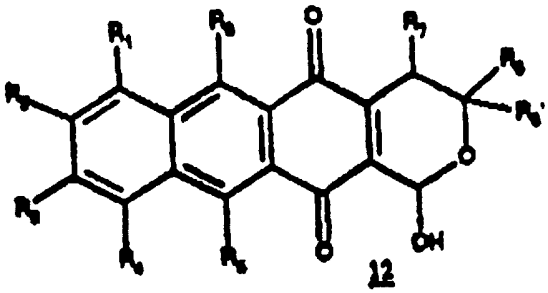
wherein R_1 to R_4 are as defined above, in the presence of a strong base in a solvent to give a tetracycle of formula (40)



40

wherein R_1 to R_6, R'_6, R_7 and R_8 are as defined above,

transforming the compound of formula (40) to the tetracyclic intermediate of formula (12),

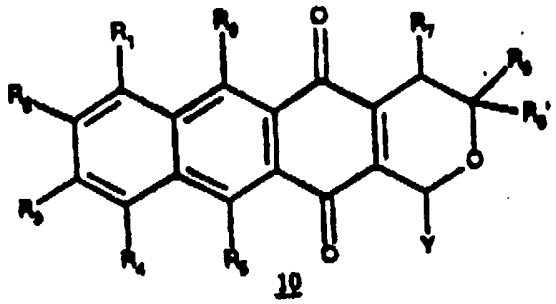


12

wherein R_1 to R_6, R'_6, and R_7 and R_8 are as defined above,

converting the intermediate of formula (12) into

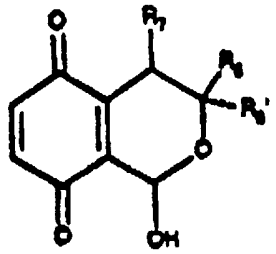
the compound of formula (10)



10

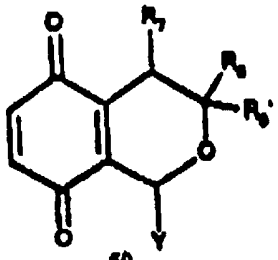
wherein R_1 to R_6, R_6', R_7, R_8 and Y are as defined above, via interconversion of the hydroxyl group in the compound of formula (12) into a group Y, as defined herein, by known methods.

188. A process according to claim 205, wherein the compound of formula (34)



34

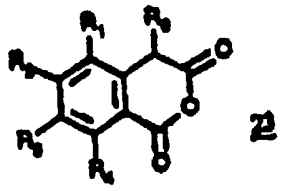
wherein R_6, R'_6 and R_7 is as defined above, is converted into an isochromandione of formula (59)



59

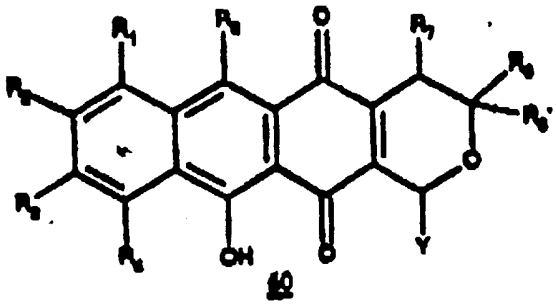
wherein R'_6, R_6, R_7 and Y are as defined herein, by transforming the hydroxyl from compound (34) into one of the groups defined for Y by using known methods,

reacting the compound of formula (59) with an homophthalic anhydride of formula (23)



22

wherein R_1 to R_4 and R_8 are as defined herein, in the presence of a strong base to give a tetracyclic derivative of formula (60)



60

wherein R_1 to R_4, R'_6, R_6 to R_8 and Y are as defined herein, and

converting the compound of formula (60) to a compound of formula (10) by known methods.

DATED THIS 10th DAY OF JUNE 1991

PATENT AGENT