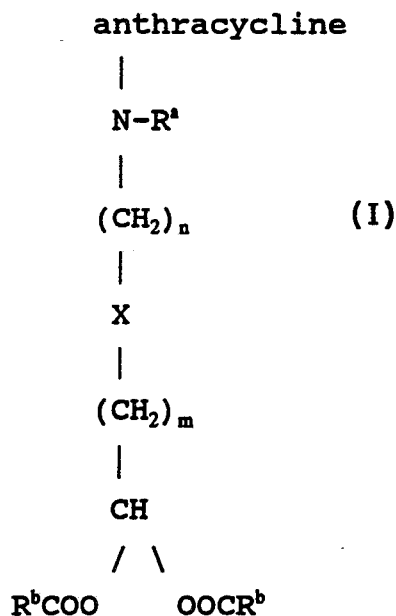




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(54) Title: ANTHRACYCLINE ANALOGUES BEARING LATENT ALKYLATING SUBSTITUENTS



(57) Abstract

2

The present invention is a compound having structure (I) where: anthracycline is doxorubicin, daunorubicin or a derivative thereof; N is the 3' nitrogen of daunosamine; R^a is H or alkyl; X is O, S, CR^c₂ or NR^c where R^c is H or alkyl; R^b is alkyl or aryl; n is 1 to 6; and m is 0 to 6. R^a and R^c are preferably H, methyl, ethyl, propyl or butyl, although other alkyl substituents are usable. R^b is alkyl or aryl. The compound of the present invention as described above is activatable *in vivo* by esterases and spontaneous dehydration to form an aldehyde. The aldehyde may couple to nucleophiles of intracellular macromolecules. The compounds of the present invention are cytotoxically effective in the inhibition of human myeloma cells.

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ANTHRACYCLINE ANALOGUES BEARING
LATENT ALKYLATING SUBSTITUENTS

This invention is in the field of anthracycline
5 chemistry. More particularly it concerns derivatives of
the anthracyclines, doxorubicin and daunorubicin, that
are useful as antitumor agents.

Daunorubicin is used for the treatment of certain
10 leukemias. Doxorubicin (adriamycin) is one of the most
useful anticancer drugs in use at this time. Doxorubicin
is a principle agent in the treatment of an unusually
wide number of solid tumors and leukemias. Regrettably,
many patients with these tumors fail to respond and
15 essentially no patients with certain serious tumor types
(colon cancer, melanoma) are successfully treated.
Additionally, in some patients chronic adriamycin
treatment produces irreversible heart damage that can be
fatal if continued. Thus, there is great need for
20 analogues which give a better rate of response, a wider
spectrum of response, and/or reduced cardiotoxicity.
More effective and less toxic agents are widely sought
and are a fundamental object of this invention.

25 Much of the history and prior art of doxorubicin and
its anthracycline analogues is found in the article
"Adriamycin" by David W. Henry, *ACS Symposium Series, NO.*
30, Cancer Chemotherapy, American Chemical Society, pp.
15-57 (1976) and in the book *Doxorubicin* by Frederico
30 Arcamone, Academic Press, 1981. The derivative AD32 is
disclosed in U.S. Pat. NO. 4,035,566, dated July 12,
1977.

5-Iminodaunorubicin is shown in U.S. Pat. No.
35 4,109,076 which issued on August 22, 1978, to David W.
Henry and George L. Tong. The doxorubicin equivalent is

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shown in "Synthesis and Preliminary Antitumor Evaluation of 5-Iminodoxorubicin", *J. Med. Chem.* 24, 669 (1981) by Edward M. Acton and George L. Tong. 5-Iminodoxorubicin retained activity with reduced side effects with 5-
5 Iminodoxorubicin showed enhanced activity but required higher dosages.

3'-Deamino-3-(4-morpholinyl)daunorubicin is described in U.S. Pat. No. 4,301,277 issued on Nov. 17.
10 1981 to Acton et al. It was active at one-fortieth the dose of doxorubicin but gave a substantially identical T/C value (166% vs 160% against P388). This compound and its preparation and properties are also disclosed in
"Enhanced Antitumor Properties of 3'-(4-Morpholinyl) and
15 3'-(4-Methoxy-1-piperidinyl) Derivatives of 3'Deaminodaunorubicin", *J. Med. Chem.*, 25, pp. 18-24 (1982) by Mosher et al.

A general reductive alkylation process for preparing
20 certain new semi-synthetic anthracycline derivatives is described in "Adriamycin Analogues. 3. Synthesis of N-Alkylated Anthracyclines With Enhanced Efficacy and Reduced Cardiotoxicity", *J. Med. Chem.*, 22 pp. 912-918 (1979) by Tong et al.

25

A group of daunorubicin and doxorubicin derivatives is disclosed in U.S. Pat. No. 4,585,859, issued April 29, 1986. Included in this group are 3'-deamino-3'-(3"-cyano-4"-morpholinyl doxorubicin; 3'-deamino-3'(3"-cyano-
30 4"-morpholinyl)-13-dihydrodoxorubicin; (3'-deamino-3'-(3"-cyano-4"-morpholinyl)-3-dihydrodaunorubicin; and 3'-deamino-3'-(4"-morpholinyl-5-iminodoxorubicin and derivatives thereof which have activity as antitumor agents.

35

U.S. Patent No. 4,841,085, June 20, 1989, by one of the present inventors, describes diacetatopropyl phosphoramidic mustard derivatives activatable *in vivo* by endogenous esterases.

5

U.S. patent 4,826,964 issued May 2, 1989 to Acton et al. describes cyanomorpholino doxorubicin which contains an esterified hydroxyl group on the morpholino group. There appears to be little, other than general classification, in common between this compound and those of the present invention.

10

U.S. 4,755,619 issued July 5, 1988 to Creighton et al. discusses a multifunctional compound which is a derivatized dicarbonylalkyl N-substituted drug which may be activated *in vivo* by hydrolysis of an ester group. This is indirectly related to the compound of the present invention but is chemically quite different. It is suggested, see column 9, lines 20-30, that the subject compounds and anthracyclines such as doxorubicin may be advantageously used together to treat cancer synergistically while avoiding the cardiotoxicity of the doxorubicin. While there was some analogy in chemical structure and *in vivo* activation, this reference does not seriously detract from the patentability of the present invention.

15

20

25

The Tsuchiya et al. reference (J. Antibiotics, July 1988, 988-991) describe doxorubicin derivatives with excellent activities against L1210 leukemia and lowered toxicities as compared to doxorubicin. These derivatives, although having ester linkages, are nonanalogous to those of the present invention.

30

35

The Acton et al. reference (J. Med. Chem. 1986, 29, 2120-2122) describes cyanomorpholinyl doxorubicin

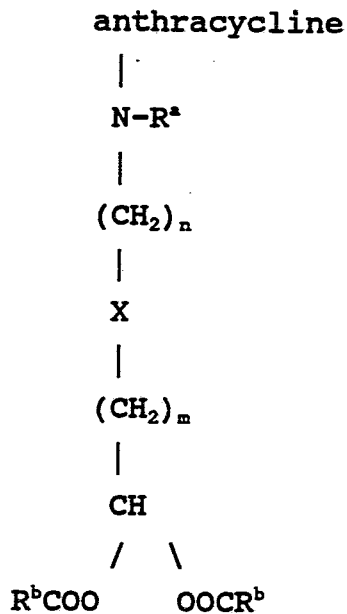
compounds and their properties.

The Horton and Priebe reference (J. Antibiotics, XXXVI, 1211-1215, 1983) describes a range of esterified anthracycline derivatives. None of these derivatives has the bis-acetal substituents of the present invention.

The Tong et al. reference (J. Med. Chem. 8, 912-918, 1979) describes various N-alkyl and N,N-dialkyl anthracyclines and their 13-dihydro derivatives.

The pertinent subject matter of the above references is specifically incorporated herein by reference.

The present invention is a compound having the structure



2

where:

anthracycline is doxorubicin, daunorubicin or a derivative thereof;

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N is the 3' nitrogen of daunosamine;
R^a is H or alkyl;
X is O or S, CR^c, or NR^c, where R^c is H or alkyl;
R^b is alkyl or aryl;
5 n is 1 to 6; and
m is 0 to 6.

R^a and R^c are preferably and independently H, methyl,
ethyl, propyl or butyl. R^b when an alkyl is preferably
10 methyl, ethyl, propyl or butyl, although other alkyl
substituents are usable. The compound of the present
invention as described above is activatable *in vivo* by
esterases and spontaneous dehydration to form an
aldehyde. The aldehyde may couple to nucleophiles of
15 intracellular macromolecules. The compounds of the
present invention are cytotoxically effective in the
inhibition of human leukemia myeloma cells.

Fig. 1 schematically describes potentially
20 alkylating derivatives of doxorubicin.

Fig. 2 schematically describes preferred compounds
of the present invention.

25 Fig. 3 schematically describes the activation
mechanism for the compounds of the present invention.

Fig. 4 generically describes a synthetic scheme for
an embodiment of the present invention.

30

The anthracycline antibiotic doxorubicin is
effective in the palliative management of a wide variety
of human malignancies¹. However, the clinical utility of
doxorubicin is limited by a number of problems, including
35 intrinsic and acquired drug resistance and dose-dependent
cardiomyopathy. Numerous analogues have been synthesized

in an attempt to overcome these shortcomings.²⁻⁴ A series of derivatives in which the 3'-amino group of the daunosamine sugar is replaced with a morpholino substituent has been reported by Acton and coworkers.⁵⁻⁷

5 One of these analogues, 3'-deamino- 3'-(3-cyano-4-morpholinyl)-adriamycin (MRA-CN) is 100 to 1000 times more cytotoxic than doxorubicin *in vitro*⁷⁻¹⁰ and *in vivo*^{6,11} and retains its potency against several tumor cell lines with acquired resistance to doxorubicin.^{9,12,13}

10

The compounds of the present invention, bis(acyloxy) acetals of an anthracycline such as doxorubicin (adriamycin), for example, are designed to be relatively stable, non-toxic but subject to activation by *in vivo* enzymes (esterases) to form an aldehyde hydrate from the
15 bis (acyloxy) acetal. This aldehyde hydrate is labile and eliminates water to form an aldehyde. By varying the composition of the anthracycline bisacyloxy-bearing side chain, many different analogues are possible, all of
20 which will be activatable at various rates by endogenous esterases and spontaneous decompositions to form active anthracycline aldehyde derivatives. It is possible to vary the composition of the side chain in both composition and length to prepare a series of such
25 analogues having desired specificities and/or non-toxicities toward particular biological sites. The side chain connecting the anthracycline and the bis acyloxy substituent will comprise at least one methylene (CH₂) group and may contain up to 9 such groups. When more
30 than one methylene group is present there may be an additional spacer group such as O, S or NR^a where R^a is H or alkyl with usually less than 5 carbon atoms, depending upon the particular properties desired.

35

A series of analogues, 1, (Fig. 1) bearing alkylating or latent alkylating substituents, R, on the

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3'-position of the daunosamine sugar were prepared. These compounds were designed on the premise that alkylating anthracyclines should bind covalently to critical intracellular macromolecules and overcome
5 resistance to doxorubicin arising from reduced cellular drug accumulation. However, in growth inhibitory studies against mouse (L1210 and P388) and human (uterine sarcoma, myelocytic) tumor cells *in vitro*, these analogues were 5- to 100-fold less potent than the parent
10 compound (doxorubicin). These analogs nevertheless did retain their cytotoxic activity against variants of these same cell lines which were resistant to doxorubicin.

To identify new alkylating anthracyclines with
15 increased potency, a series of doxorubicin analogues was synthesized in which the 3'-amino group is substituted with a latent alkanal or heteroalkanal group. A rationale for the design of these compounds was that: (a) the latent alkanal or heteroalkanal groups would be
20 converted to the corresponding free aldehydes when the drugs were placed in a biological medium (such as cells or whole organisms), and (b) the liberated free aldehydes would react with nucleophiles (such as amino or sulfhydryl groups) proximate to the DNA drug-binding site
25 to form covalent adducts. As a consequence, drug egress from the cell should be inhibited.

Because of the intrinsic chemical reactivity of free aldehydes, the alkanal (or heteroalkanal) groups were
30 introduced into the doxorubicin molecule in latentiated form. Bis(acyloxy) groups were selected for this purpose. The general structure of the new doxorubicin analogues is shown in Fig. 2, where the anthracycline is doxorubicin or daunorubicin.

Additionally, the acyloxy group may be varied. For example, the acyloxy group may be acetate, propionate, butyrate (n or t) or even benzoate or substituted benzoate. The acyloxy substituent may also be varied to
5 control the rate of drug activation resulting from ester hydrolysis. For example, certain sterically hindered ester groups may be hydrolyzed much less rapidly than a simpler substituent such as acetoxy.

10 The mechanism for regeneration of the free aldehyde is illustrated in Figure 3 with respect to compound 2a (Fig. 2 n = 2, m = 1, X = CR^c₂ where R^c is H, R^b = CH₃ and R^a = H). In the presence of carboxylate esterases, enzymes that are ubiquitous in tissue, and which show low
15 substrate specificity, compound 2a can be hydrolyzed to the corresponding aldehyde hydrate, 3a. Elimination of water from 3a generates the free aldehyde, 4a. The aldehyde group can then react with a nucleophile such as one on a macromolecule proximate to, or within, a DNA-
20 binding site to form a potential covalent drug-DNA adduct, 5a.

Apart from recent studies by the inventors' laboratory with cyclophosphamide metabolites (see U.S.
25 4,841,085 and Aldophosphamide bis(acetoxy)acetal and Structural Analogues. J. Med. Chem., In Press, 1990, for example) this approach to the bioreversible latentiation of aldehydes has not been described previously and has not at all been described before for anthracycline
30 derivatives.

An important aspect of this strategy is that by judicious selection of the acyloxy groups, it should be possible to modify the lipophilicity and aqueous
35 solubility of these analogues. Moreover, since these compounds are designed to be activated by carboxylate

esterases (enzymes present in all cells), the acyloxy masking groups can be altered to control the rate at which the active "alkylating" anthracyclines are formed.

5 A number of compounds having the general structure 2 have been prepared. These were synthesized by condensing doxorubicin with a dialdehyde monoacetal then reducing the intermediate imine with NaBH_3CN . The overall synthetic strategy can be exemplified with respect to 2a
10 as schematically illustrated in Figure 4.

To the best of applicants' knowledge, dialdehyde monoacetals such as 10 have not been reported previously. [These should be versatile synthetons in organic
15 synthesis since the acetal ester groups can be cleaved under extremely mild conditions (weak base or esterase activity)]. Condensation of 10 with doxorubicin, 11, in the presence of NaCNBH_3 generated 2a directly in > 50% yield. Evidence for the structure of 2a was obtained by
20 ^1H and COSY NMR, and by mass spectrometry. The compound is freely soluble in aqueous media and is stable at neutral pH.

To investigate structure-activity relationships for
25 this class of compounds, the analogs (based upon structure 2 of Fig. 2) shown in Table 1 have been prepared.

Table 1

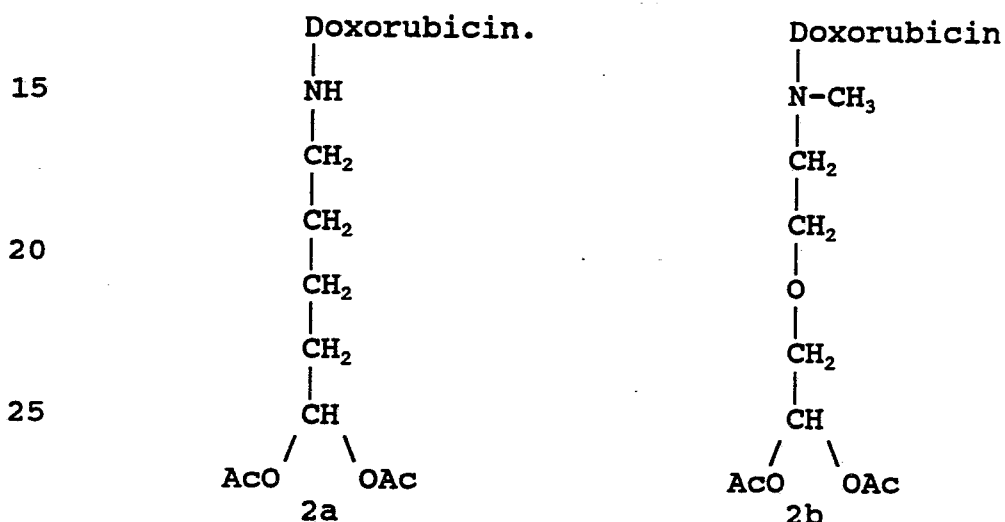
30

2a	$n = 2,$	$m = 1,$	$X = \text{CH}_2,$	$\text{R}^b = \text{CH}_3,$	$\text{R}^a = \text{H}$
2b	$n = 2,$	$m = 1,$	$X = \text{O},$	$\text{R}^b = \text{CH}_3,$	$\text{R}^a = \text{CH}_3$
2c	$n = 2,$	$m = 0,$	$X = \text{CH}_2,$	$\text{R}^b = \text{CH}_3,$	$\text{R}^a = \text{H}$
2d	$n = 2,$	$m = 2,$	$X = \text{CH}_2,$	$\text{R}^b = \text{CH}_3,$	$\text{R}^a = \text{H}$
35 2e	$n = 2,$	$m = 0,$	$X = \text{C}(\text{CH}_3)_2,$	$\text{R}^b = \text{CH}_3,$	$\text{R}^a = \text{H}$
2f	$n = 2,$	$m = 2,$	$X = \text{O},$	$\text{R}^b = \text{CH}_3,$	$\text{R}^a = \text{H}$
2g	$n = 2,$	$m = 4,$	$X = \text{CH}_2,$	$\text{R}^b = \text{CH}_3,$	$\text{R}^a = \text{H}$

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This strategy obviously may be readily extended to the synthesis of a series of analogues where, e.g., X = O, S, NR^c or CR₂, where R^c is H or alkyl; n = 1-6; m = 0-6; R^a = H, CH₃, C₂H₅, C₃H₇, or other hydrocarbons (C_xH_{2x+1}); and R^b = CH₃, C₂H₅, C₃H₇, or C(CH₃)₃. While hydrochloride salts have been prepared, it is well known to utilize other pharmaceutically acceptable acids in place of hydrochloric acid to make numerous pharmaceutically acceptable salts.

10

EXAMPLE 1**Cytotoxicity Studies**

30

Table 2

Compound	IC ₅₀ ^a (nM)	
	CEM ^b cells	CEM(VLB) ^c cells
Resistance index ([CEM(VLB)]/[CEM])		
Doxorubicin	10	1340
134		
Compound 2a	0.15	16
Compound 2b	3	15
5		

^a Determined after six days incubation with drug at 37°C

^b A human T-lymphoblastic cell line

^c A human T-lymphoblastic cell line resistant to

45

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Velban (vinblastine)

Compound 2a was 60 times more toxic to the parent
5 CEM cells than doxorubicin, and showed markedly reduced
cross resistance against the velban resistant mutant.

In related studies compound 2a was shown to be 400
times more potent ($IC_{50} = 1.5$ nM) to 8226R40 human myeloma
10 cells than doxorubicin ($IC_{50} = 600$ nM).

EXAMPLE 2**Synthetic and Related Methods Experimental**

15 Nuclear magnetic resonance spectra (1H and ^{13}C) were
recorded at ambient temperature on an IBM-Bruker Model
NR/200 AF spectrometer in the Fourier transform mode in
CDCl₃ with tetramethylsilane as an internal reference.
Chemical shifts (δ) are reported in parts per million
20 (ppm) and coupling constants (J) in hertz units.
Specialist NMR techniques used for structural assignment
include: off-resonance decoupling plus single frequency,
selective heteronuclear decoupling, homonuclear shift-
correlated 2D-NMR (COSY), homonuclear shift-correlated
25 2D-NMR with a delay period to emphasize long range or
small coupling (COSYLR), and heteronuclear shift-
correlated 2D-NMR using polarization transfer from 1H to
 ^{13}C via J_{CH} (XH-CORR). Mass spectral analyses were
conducted at TexMS, 15701 West Hardy Road, Houston, Texas
30 using an atmospheric pressure desorption technique. All
chemical reactions were carried out in dry glassware and
were protected from atmospheric moisture. Solvents were
dried over freshly activated (300°C/1 h) molecular sieves
(type 4 A). Evaporations were carried out on a rotary
35 evaporator under aspirator vacuum at a bath temperature
of < 25°C. The homogeneity of the products was

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determined by ascending TLC on silica-coated glass plates (silica gel 60 F 254, Merck) using mixtures of CHCl_3 -MeOH as the eluting solvent. Preparative separations were performed on thick layers (20 cm x 20 cm x 2 mm) of the same adsorbent or by column chromatography on silica gel (Merck, 230-400 mesh) using mixtures of CHCl_3 -MeOH as eluent.

10 Preparation of 5-Hexen-1-al (8):

- Method A:

 A solution of the Jones reagent¹⁶ in acetone (10 mL, 2.67 M) was added, dropwise, with stirring over 10 min to a solution of 5-hexen-1-ol (6) (2 mL, 1.67 g, 17 mmol) in acetone (5 mL) at 0°C. The reaction mixture was maintained at 5°C for 1 h. Saturated NaHCO_3 solution was added to bring the pH to 7.0 and the mixture was extracted with CHCl_3 (3 x 20 mL). The combined extracts were washed with H_2O (3 x 20 mL), and dried over anhydrous Na_2SO_4 . The solvent was evaporated to give a crude product, which was then purified by filtering-column chromatography on silica gel (98:2 CHCl_3 /MeOH) to give 0.98 g (10 mmol) of pure 5-hexen-1-al (8) as a colorless oil. Yield 59%.

¹H NMR [chemical shift (o), multiplicity, coupling constant (Hz), number of protons, atom]: 9.71 (t, J = 1 Hz, 1 H, H-1), 5.75 (m, 1 H, H-5), 5.04 (m, 2 H, H-6), 2.45 (m, 2 H, H-2), 2.08 (m, 2 H, H-4), 1.72 (m, 2 H, H-3).

¹³C NMR (ppm, atom): 201.95 (C-1), 137.18 (C-5), 115.07 (C-6), 42.67 (C-2), 32.55 (C-4), 20.75 (C-3).

- Method B:

A solution of 5-hexen-1-ol (6) (2 mL, 1.67 g, 17 mmol) in CH₂Cl₂ (5 mL) was added in one portion to a stirred solution of pyridinium chlorochromate¹⁶ (5.5 g, 5 25.5 mmol) in anhydrous CH₂Cl₂ (35 mL) contained in a 100 mL round bottomed flask fitted with a reflux condenser. After 2.5 h at ambient temperature, dry ether (40 mL) was added. The organic supernatant was decanted and the residual black gum was triturated with anhydrous ether (3 10 x 10 mL) until a black granular solid remained. The organic extracts were combined, filtered through a short pad of florisil, then concentrated under reduced pressure. The residual liquid was passed through a short Vigreux column to give 1.37 g of pure 5-hexen-1-al (8) 15 (14 mmol, 82%).

The spectral properties of the compound were identical with that of the product obtained by Method A.

20

- Method C:

4A powdered molecular sieves (500 mg/mmol, 8.5 g) was added to a solution of 5-hexen-1-ol (6) (2 mL, 1.67 25 g, 17 mmol) and N-methylmorpholine N-oxide (1.5 eq., 25.6 mmol, 3.4 g) in CH₂Cl₂ (35 mL). The mixture was stirred for 10 min at room temperature under a nitrogen atmosphere then tetrapropyl-ammonium perruthenate (TPAP)¹⁷ (0.30 g, 0.85 mmol, 5 mol%) was added in one portion. 30 The initially green mixture progressively darkened. The reaction was completed after 2h at room temperature (as evidenced by TLC), CH₂Cl₂ (35 mL) was added and the mixture was passed first through a short pad of filter agent, (Celite). The filtrate was evaporated and the 35 residual crude was purified by filtering-column chromatography on silica gel (98:2, CHCl₃/MeOH) to afford

1.47 g of pure 5-hexen-1-al (8) (15 mmol, 88%).

The spectral properties of the compound were identical with that of the product obtained by Method A.

5

Since the TPAP oxidation procedure gave the best yields and was the most convenient, it was used for all subsequent procedures for the preparation of aldehydes from the corresponding alcohols.

10

4-Penten-1-al (13):

This product was prepared from:

15

a: 4-Penten-1-ol (12) (1.76 mL, 1.46 g, 17 mmol) as described for 5-hexen-1-al (8), Method C. The total yield of the desired aldehyde (13) was 91%, (15.58 mmol, 1.31 g).

20

¹H NMR: 9.91 (t, J = 1 Hz, 1 H, H-1), 5.80 (m, 1 H, H-4), 5.21 (m, 2 H, H-5), 2.12 (m, 2 H, H-2), 1.95 (m, 2 H, H-3).

25

¹³C NMR: 200.28 (C-1), 137.61 (C₄), 114.96 (C-5), 32.80 (C-2), 32.21 (C-3).

b: 5-Hexen-1,2-diol (2.24 mL, 2.2 g, 18.9 mmol) was added slowly, with stirring, over 10 min to a solution of NaIO₄ (4.1 g) in water (45 mL) under ice cooling, and then left at room temperature for 2 h. Ethanol (30 ml) was added and the mixture was filtered to remove precipitated sodium salts, and concentrated. Chloroform (50 ml) and H₂O (20 ml) were added, and the organic layer was separated, dried, filtered, and evaporated to dryness. The residue was chromatographed on silica gel (96:4

35

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CHCl₃/MeOH) to give 4-penten-1-al (13) as a colorless liquid (1.2 g, 14.2 mmol, 75%).

The spectral properties of the compound were
5 identical with that of the product obtained by method a.

6-Hepten-1-al (18):

10 This product was prepared from 6-hepten-1-ol (17) (1.9 g, 17 mmol), as described for 5-hexen-1-al (8), Method C. The total yield of the desired (18) was 90%, (15.3 mmol, 1.72 g).

15 ¹H NMR: 9.62 (s, 1 H, H-1), 5.83 (m, 1 H, H-6), 4.92 (m, 2 H, H-7), 2.41 (t, 2 H, J = 7.1 Hz, H-2), 1.74 (m, 2 H, H-3), 1.51 (m, 2 H, H-5), 1.35 (m, 6 H, H-4) .

¹³C NMR: 202.51 (C-1), 138.04 (C-6), 114.67 (C-7),
20 43.44 (C-2), 33.43 (C-5), 28.13 (C-3), 24.81 (C-4).

8-Nonen-1-al (22):

This product was prepared from 8-nonen-1-ol¹⁸(21)
25 (2.4 g, 17 mmol) as described for 5-hexen-1-al (8), Method C. The residue was subjected to a column chromatography on silica gel (98:2 CHCl₃/MeOH), yielding 2.12 g as a syrup (15.13 mmol, 89%) of (22).

30 ¹H NMR: 9.65 (s, 1 H, H-1), 5.72 (m, 1 H, H-8), 4.95 (m, 2 H, H-9), 2.43 (t, 2 H, J = 5 Hz, H-2), 2.12 (m, 2 H, H-7), 1.54 (m, 2 H, H-3), 1.33 (m, 6 H, H-4, H-5, H-6).

35 ¹³C NMR: 200.54 (C-1), 138.82 (C-8), 114.11 (C-9), 35.01 (C-2), 34.24 (C-7), 28.83 (C-3), 28.74 (C-6), 23.92

(C-4), 23.24 (C-5).

3-(Allyloxy)propionaldehyde (25):

5

A solution of allyl alcohol (30 mL, 25.6 g, 0.44 mol), monochloroacetic acid (3 g, 0.032 mol), and sodium hydroxide (1.27 g, 0.032 mol) in H₂O (5 mL) was added dropwise, with stirring over 10 min to acrolein (80 mL, 1.2 mol) contained in a 250 ml flask. Acetic acid (12 mL, 0.21 mol) was added and the reaction mixture was maintained at 40°C for 40 h. After cooling to room temperature, the mixture was washed with H₂O (50 mL x 3), and the organic layer was dried over anhydrous Na₂SO₄. The solution was concentrated under aspirator vacuum at 40°C to remove volatile by-products. The residual viscous oil was purified by column chromatography on silica gel using CH₂Cl₂ as a eluent to give 34.2 g of (25) (0.3 mol) as a colorless oil. Yield, 69%.

20

¹H NMR: 9.82 (t, 1 H, J = 1 Hz, H-1), 5.82 (m, 1 H, H-2'), 5.21 (m, 2 H, H-3'), 3.93 (dt, 2 H, J = 3, 1 Hz, H-1'), 3.82 (t, 2 H, J = 4 Hz, H-3), 2.61 (dt, 2 H, J = 4, 1 Hz, H-2).

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¹³C NMR: 202.12 (C-1), 134.24 (C-2'), 116.24 (C-3'), 71.43 (C-1'), 64.34 (C-3), 34.12 (C-2).

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5-Hexen-1,1-diacetate (9):

5-Hexen-1-ol (8) (5 g, 5.9 mL, 50.9 mmol) was added dropwise, with stirring over 5 min at ambient temperature to a solution of acetic anhydride (3 mL, 31 mmol) and BF₃·Et₂O (0.5 mL) in anhydrous Et₂O (10 mL). The reaction mixture was stirred for 10 min, then washed successively

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with 25% NaOAc solution (20 mL) and H₂O (25 mL x 2), and dried over anhydrous Na₂SO₄. The ether was evaporated and the residue was distilled to give the diacetoxy acetal (9) (9.6 g, 48 mmol, 94%). The product was used in subsequent reactions without further purification.

¹H NMR: 6.83 (t, 1 H, J = 5 Hz, H-1), 5.58 (m, 1 H, H-5), 5.02 (m, 2 H, H-6), 2.12 (s, 6 H, CH₃), 2.05 (m, 2 H, H-2), 1.85 (m, 2 H, H-4), 1.50 (m, 2 H, H-3).

¹³C NMR: 168.42 (C=OCH₃), 137.43 (C-5), 114.81 (C-6), 89.92 (C-1), 32.82 (C-2), 32.14 (C-4), 22.23 (C-3), 20.32 (CH₃).

4-Penten-1,1-diacetate (14):

The compound was prepared from 4-penten-1-al (13) (6.7 g, 7.8 mL, 80 mmol), acetic anhydride (5.7 mL, 6.13 g, 60 mmol) and BF₃.Et₂O (0.2 mL) in Et₂O (6 mL) as described for (9). After removing the excess of acetic anhydride by distillation, the residue was subjected to a column chromatography on silica gel (97:3 CHCl₃/MeOH) to give the diacetoxy acetal (14) (14 g, 75.2 mmol, 94%)

¹H NMR: 6.85 (t, 1 H, H-1, J = 5 Hz), 5.74 (m, 1 H, H-4), 4.95 (m, 2 H, H-5), 2.05 (m, 2 H, H-2), 2.03 (s, 6 H, CH_{3ac.}), 1.85 (m, 2 H, H-3).

¹³C NMR: 168.75 (C=OCH₃), 137.64 (C-4), 115.01 (C-5), 89.85 (C-1), 32.96 (C-2), 32.17 (C-3), 20.24 (CH₃).

6-Hepten-1,1-diacetate (19):

The compound was prepared from 6-heptenal (18) (4 g,

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4.7 mL, 35 mmol), acetic anhydride (2.8 mL, 3.1 g, 30 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.2 mL) in Et_2O (5 mL) as described for (9). After removing the excess of acetic anhydride by distillation, the residue was subjected to a column chromatography on silica gel (97:3 $\text{CHCl}_3/\text{MeOH}$) to give the diacetoxo acetal (19) (7.14g, 33.3 mmol, 95%)

^1H NMR: 6.87 (t, $J = 5$ Hz, 1 H, H-1), 5.83 (m, 1 H, H-6), 4.98 (m, 2 H, H-7), 2.15 (dt, $J = 5, 1$ Hz, 3 H, H-2), 2.02 (s, 6 H, $\text{CH}_{3\text{ac}}$), 1.90 (m, 2 H, H-5), 1.64 (m, 4 H, H-3, H-4).

^{13}C NMR: 168.54 (COCH_3), 137.93 (C-6), 114.92 (C-7), 89.86 (C-1), 33.43 (C-2), 33.14 (C-5), 24.52 (C-3), 21.21 (C-4), 20.22 (CH_3).

2,2-Dimethyl-4-pentene-1,1-diacetate (29):

The compound was prepared from 2,2-dimethyl-4-penten-1-al (28) (3 mL, 2.5 g, 22 mmol) acetic anhydride (1.4 mL, 1.56 g, 15 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.2 mL) in Et_2O (5 mL) as described for (9). After removing the excess of acetic anhydride by distillation, the residue was subjected to a column chromatography on silica gel (96:4 $\text{CHCl}_3/\text{MeOH}$) to give the diacetoxo acetal (29) (4.44 g, 20.7 mmol, 94%).

^1H NMR: 6.52 (s, 1 H, H-1), 5.75 (m, 1 H, H-4), 4.95 (m, 2 H, H-5), 2.05 (s, 6 H, $\text{CH}_{3\text{ac}}$), 2.02 (m, 2 H, H-3), 1.85 (s, 6 H, CH_3) ^{13}C NMR: 168.63 (COCH_3), 133.46 (C-4), 117.65 (C-5), 93.55 (C-1), 41.43 (C-3), 37.42 (C-2), 21.01 (CH_3), 20.34 ($\text{CH}_{3\text{ac}}$)

8-Nonen-1,1-diacetate (23):

The compound was prepared from 8-nonen-1-al (22) (8.3 mL, 7 g, 50 mmol), acetic anhydride (3.8 mL, 4 g, 40 mmol) and $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (0.2 mL) in Et_2O (7 mL) as described for (9). After removing the excess of acetic anhydride by distillation, the residue was subjected to a column chromatography on silica gel (97:3 $\text{CHCl}_3/\text{MeOH}$) to give the diacetoxo acetal (23) (11.75 g, 48.5 mmol, 97%).

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^1H NMR: 6.82 (t, 1 H, $J = 5.6$ Hz, H-1), 5.75 (m, 1 H, H-8), 4.95 (m, 2 H, H-9), 2.02 (s, 6 H, CH_3_{ac}), 1.98 (m, 2 H, H-7), 1.75 (m, 2 H, H-2), 1.54 (m, 2 H, H-4), 1.35 (m, 6 H, H-6, H-5, H-3).

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^{13}C NMR: 168.84 (COCH_3), 138.83 (C-8), 114.12 (C-9), 90.43 (C-1), 34.92 (C-2), 34.15 (C-7), 28.84 (C-3), 28.71 (C-6), 23.84 (C-4), 23.21 (C-5), 20.64 (CH_3).

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3-(Allyloxy)propane-1,1-diacetate (26):

The compound was prepared from 3-(allyloxy)propionaldehyde (25) (5.2 mL, 5 g, 44 mmol), acetic anhydride (2.4 mL, 25 mmol) and $\text{BF}_3/\text{Et}_2\text{O}$ (0.2 mL) in Et_2O (5 mL) as described for (9). After removing the excess of acetic anhydride by distillation, the residue was subjected to a column chromatography on silica gel (96:4 $\text{CHCl}_3/\text{MeOH}$) to give the diacetoxo acetal (26) (8.94 g, 41.4 mmol, 94%).

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^1H NMR: 6.92 (t, 1 H, $J = 4$ Hz, H-1), 5.85 (m, 1 H, H-2'), 5.23 (m, 2 H, H-3'), 3.95 (dt, 2 H, $J = 3, 1$ Hz, H-1'), 3.44 (t, 2 H, $J = 4$ Hz, H-3), 2.01 (s, 6 H, CH_3_{ac}), 1.95 (dt, 2 H, $J = 4, 2$ Hz, H-2).

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¹³C NMR: 168.02 (COCH3), 134.44 (C-2'), 116.43 (C-3'), 88.42 (C-1), 71.41 (C-1'), 64.76 (C-3), 33.25 (C-2), 20.26 (CH3).

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2-Propene-1,1-diacetate (31):

The compound was prepared from acrolein (6 mL, 5 g, 90 mmol), acetic anhydride (5.7 mL, 6.13 g, 60 mmol) and BF₃/Et₂O (0.25 mL) in Et₂O (5 mL) as described for (9) After removing the excess of acetic anhydride by distillation, the residue was subjected to a column chromatography on silica gel (97:3 CHCl₃/MeOH) to give the diacetoxy acetal (31) (13.7 g, 86.4 mmol, 96%).

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¹H NMR: 7.14 (d, J = 7 Hz, 1 H, H-1), 5.85 (m, 1 H, H-2), 5.45 (m, 2 H, H-3), 2.05 (s, 6 H, CH3).

¹³C NMR: 168.15 (COCH3), 131.12 (C-2), 119.44 (C-3), 88.76 (C-1), 20.38 (CH3).

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5-Pentanal-1,1-diacetate (10):

A solution of 5-hexen-1,1-diacetate (9) (5 g, 3.5 ml, 25 mmol) in CH₂Cl₂ (5 mL) was placed in a long cylindrical gas absorption vessel with an inlet dispersion tube extending to the base. The vessel was cooled to -70°C in a dry ice/acetone mixture, and ozone was introduced. Ozonization was continued until all of the compound had reacted (blue color due to the formation of the ozonide), approximately 20 min. Methyl sulfide (7.25 mL, 0.1 mol, 4 equivalents) was added to the blue solution of ozonide and the mixture was stirred overnight to reduce the ozonide to the corresponding aldehyde. The excess methyl sulfide was evaporated, and the residue was

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subjected to a column chromatography on silica gel (CH₂Cl₂) giving aldehyde (10) (4.29 g, 21.25 mmol, 85%) as a syrup.

5 ¹H NMR: 9.83 (t, 1 H, J = 1 Hz, H-5), 6.75 (t, 1 H, J = 5 Hz, H-1), 2.66 (dt, 2 H, J = 5.5, 1 Hz, H-4), 2.14 (s, 6 H, CH₃), 2.05 (m, 2 H, H-2), 1.85 (m, 2 H, H-3).

¹³C NMR: 201.43 (C-5), 168.72 (C=O), 89.61 (C-1),
10 42.86 (C-4), 32.10 (C-2), 20.54 (CH₃), 15.62 (C-3).

 analysis: calc'd for C₉H₁₄O₅ - c, 53.46; H 6.98.

 Found - - - - - c, 53.61; H 7.87.

4-Butanal-1,1-diacetate (15):

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The compound was prepared from 4-penten-1,1-diacetate (14) (4.65 g, 3.45 mL, 25 mmol) in CH₂Cl₂ (5 mL) as described for (10). After removing the excess of methyl sulfide by distillation, the residue was subjected
20 to a column chromatography on silica gel (CH₂Cl₂) to give the desired aldehyde (15) (4.04g, 21.5 mmol, 86%) as a colorless oil.

¹H NMR: 9.83 (t, 1 H, J = 1 Hz, H-4), 6.75 (t, 1 H, J = 5 Hz, H-1), 2.66 (dt, 2 H, J = 5.5, 1 Hz, H-3), 2.14 (s, 6 H, CH₃), 2.05 (m, 2 H, H-2).

¹³C NMR: 201.43 (C-4), 168.72 (C=O), 89.61 (C-1),
30 42.86 (C-3), 32.10 (C-2), 20.54 (CH₃).

6-Hexanal-1,1-diacetate (20):

The compound was prepared from 6-hepten-1,1-diacetate (19) (5.35 g, 3.5 mL, 25 mmol) in CH₂Cl₂ (5 mL) as described for (10). After removing the excess of
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Methyl sulfide by distillation, the residue was subjected to a column chromatography on silica gel (CH_2Cl_2) to give the desired aldehyde (20) (4.71g 21.8 mmol, 87%) as a colorless oil.

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^1H NMR: 9.83 (t, 1 H, $J = 1$ Hz, H-6), 6.75 (t, 1 H, $J = 5$ Hz, H-1), 2.66 (dt, 2 H, $J = 5.5, 1$ Hz, H-5), 2.14 (s, 6 H, CH_3), 2.05 (m, 2 H, H-2), 1.85 (m, 2 H, H-3), 1.82 (m, 2H, H-4).

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^{13}C NMR: 201.43 (C-6), 168.72 (COCH_3), 89.61 (C-1), 42.86 (C-5), 32.10 (C-2), 20.54 (CH_3), 15.62 (C-3), 15.60 (C-4).

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8-Octanal-1,1-diacetate (24):

The compound was prepared from 8-nonen-1,1-diacetate (23) (6.05 g, 25 mmol) in CH_2Cl_2 (5 mL) as described for (10). After removing the excess of Methyl sulfide by distillation, the residue was subjected to a column chromatography on silica gel (CH_2Cl_2) to give the desired aldehyde (24) (5.12g, 21 mmol, 84%) as a colorless oil.

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^1H NMR: 9.83 (t, 1 H, $J = 1$ Hz, H-8), 6.75 (t, 1 H, $J = 5$ Hz, H-1), 2.66(dt, 2 H, $J = 5.5, 1$ Hz, H-7), 2.14 (s, 6 H, CH_3), 2.05 (m, 2 H, H-2), 1.85 (m, 2 H, H-3), 1.82-1.75 (m, 6H, H-4, H-5, H-6).

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^{13}C NMR: 201.50 (C-8), 168.70 (COCH_3), 89.66 (C-1), 42.88 (C-7), 32.15 (C-2), 20.58 (CH_3), 15.62 (*C-3), 15.60 (*C-4), 15.46 (*C-5), 15.00 (*C-6).

* Assignments for C_3 , C_4 , C_5 and C_6 may be interchanged.

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O-(3,3-diacetoxypropyl)glycolaldehyde (27):

The compound was prepared from 3-(allyloxy)propane-
1,1-diacetate (26) (5.4 g, 25 mmol) in CH₂Cl₂ (5 mL) as
described for (10). After removing the excess of Methyl
sulfide by distillation, the residue was subjected to a
column chromatography on silica gel (CH₂Cl₂) to give the
desired aldehyde (27) (4.58 g, 21 mmol, 84%) as a
colorless oil.

¹H NMR: 9.63 (t, 1 H, J = 1 Hz, H-1'), 6.74 (t, 1 H,
J = 4.2 Hz, H-1), 4.27 (d, 2 H, J = 1 Hz, H-2'), 3.45 (t,
2 H, J = 4.2 Hz, H-3), 2.01 (s, 6 H, CH_{3ac}), 1.95 (dt, 2 H,
J = 4, 2 Hz, H-2).

¹³C NMR: 199.94 (C-1'), 168.35 (C=O), 88.37 (C-1),
72.32 (C-2'), 64.66 (C-3), 33.35 (C-2), 20.36 (CH₃).

Analysis Calc'd for C₉H₁₄O₆: C, 49.54; H, 6.47.

Found: C, 49.51; H, 6.58.

2,2-Dimethyl-4-butanal-1,1-diacetate (30):

The compound was prepared from 2,2-dimethyl-4-
pentene-1,1-diacetate (29) (5.32 g, 3.54 mL, 25 mmol) in
CH₂Cl₂ (5 mL) as described for (10). After removing the
excess of Methyl sulfide by distillation, the residue was
subjected to a column chromatography on silica gel
(CH₂Cl₂) to give the desired aldehyde (30) (4.68 g, 21.8
mmol, 87%) as a colorless oil.

¹H NMR: 9.85 (t, 1 H, J = 1 Hz, H-4), 6.65 (t, 1 H, J
= 5 Hz, H-1), 2.08 (s, 6 H, CH_{3ac}), 2.01 (m, 2 H, H-3),
1.85 (s, 6 H, CH₃).

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^{13}C NMR: 201.05 (C-4), 168.72 ($\text{C}=\text{OCH}_3$), 89.65 (C-1), 42.80 (C-3), 37.42 (C-2), 21.50 (CH_3), 20.35 (CH_3).

Analysis Calc'd. for $\text{C}_{10}\text{H}_{16}\text{O}_5$: C, 55.55; H, 7.46.

Found: C, 54.67; H, 7.55.

O-(2,2-diacetoxyethyl)glycolaldehyde (35):

This compound was prepared in four steps from anhydrous glycerol by monoalkylation, oxidation of the diol, acetylation and ozonolysis

- 3-Allyloxy-1,2-propandiol (32):

KOH (11.2 g, 200 mmol) was added cautiously to anhydrous glycerol (60 mL, 821 mmol) in a 250 mL flask, and the mixture was heated to 60°C under a nitrogen atmosphere until the KOH had dissolved. After cooling to room temperature, allyl bromide (17.3 mL, 20 mmol) was added over 15 min, dropwise with stirring and the mixture was stirred at 90°C for 14 h. After cooling to room temperature, the mixture was diluted with aqueous 50% K_2CO_3 (100 mL) then extracted with CH_2Cl_2 (3 x 100 mL). The combined extracts were dried, filtered and evaporated. The residual diol, a colorless oil, 22.5 g (32) (170 mmol, 85%), was used for subsequent reaction without further purification.

^1H NMR: 5.92 (m, 1 H, H-2'), 5.21 (m, 2 H, H-3'), 4.14 (m, 1 H, H-2), 3.97 (m, 2 H, H-3), 3.79 (m, 2 H, H-1'), 3.71 (m, 2 H, H-1).

^{13}C NMR: 134.19 (C-2'), 117.18 (C-3'), 72.09 (C-1'), 71.11 (C-1), 70.74 (C-2), 63.72 (C-3).

- 2-Allyloxyethan-1-al (33):

This diol (32) (1.71 mL, 2.5 g, 18.9 mmol) was added slowly, with stirring, over 10 min to a solution of NaIO₄ (4.1 g) in water (45 mL) under ice cooling and then left at room temperature for 2 h. Ethanol (30 ml) was added and the mixture was filtered to remove precipitated sodium salts, and concentrated. Chloroform (50 ml) and H₂O (20 ml) were added, and the organic layer was separated, dried, filtered, and evaporated to dryness. The residue was chromatographed on silica gel (96:4 CHCl₃/MeOH) to give allyloxy glycol aldehyde (33) as a colorless liquid (1.32 g, 13.2 mmol, 70%).

¹H NMR: 9.73 (t, 1 H, J = 1 Hz, H-1), 5.95 (m, 1 H, H-2'), 5.37 (m, 2 H, H-3'), 4.05 (m, 4 H, H-1, H-2).

¹³C NMR: 199.86 (C-1), 133.32 (C-2'), 117.02 (C-3'), 74.65 (C-2), 71.64 (C-1').

- 2-Allyloxyethane-1,1-diacetate (34):

The aldehyde (33) (1.32 g, 13.2 mmol) was added dropwise, with stirring, over 5 min at ambient temperature to a solution of acetic anhydride (1.5 mL, 16.5 mmol), Et₂O (5 mL) and BF₃·Et₂O (0.1 mL). The reaction mixture was stirred for 10 min then washed successively with 25% NaOAc solution (5 mL) and H₂O (10 mL x 2), and dried over anhydrous Na₂SO₄. After removing the excess of acetic anhydride by distillation, the residue was subjected to a column chromatography on silica gel (97:3 CHCl₃/MeOH) to give the diacetoxycetal(34) (2.55 g, 12.6 mmol, 95%).

¹H NMR: 6.82 (t, 1 H, J = 5 Hz, H-1), 5.75 (m, 1 H, H-2'), 5.15 (m, 2 H, H-3'), 3.98 (m, 2 H, H-1'), 3.55 (d,

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2 H, $J = 5$ Hz, H-2), 2.09 (s, 6 H, CH₃).

¹³C NMR: 168.33 (C=OCH₃) 133.74 (C-2'), 117.21 (C-3'), 87.34 (C-1), 72.04 (C-1'), 68.53 (C-2), 20.31 (CH₃).

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- O-(2,2-diacetoxyethyl)glycolaldehyde (35):

The diacetoxy acetal (34) (2.55 g, 12.6 mmol) in CH₂Cl₂ (5 mL) was ozonized as described for compound (10).
10 Methyl sulfide (3.7 mL, 50.5 mmol, 4 equiv.) was added to the blue ozonide solution and the mixture was stirred overnight. Evaporation of solvent and unreacted methyl sulfide, and chromatography on silica gel (CH₂Cl₂ eluent) gave the corresponding aldehyde (35), (2.21 g, 10.84
15 mmol, 86%).

¹H NMR: 9.62 (t, 1 H, $J = 1$ Hz, H-1'), 6.84 (t, 1 H, $J = 5.2$ Hz, H-1), 4.23 (d, 2 H, $J = 1$ Hz, H-2'), 3.86 (d, 2 H, $J = 5.2$ Hz, H-2), 2.01 (s, 6 H, CH₃).

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¹³C NMR: 199.94 (C-1'), 168.35 (C=OCH₃), 87.37 (C-1), 72.32 (C-2'), 68.51 (C-2), 20.35 (CH₃).

Analysis calc'd. for C₈H₁₂O₆: C, 47.06; H, 5.92.

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Found: C, 46.84; H, 5.81.

Ethyl allyl-4-butyrate (16):

A solution of heptenoic acid (1.1 mL, 1 g, 7.8 mmol)
30 in ethanol (2 mL) was added to a stirred solution of p-toluene sulfonic acid (0.19 g, 1 mmol) in ethanol (10 mL). The mixture was stirred at 60°C for 2 h, then allowed to cool to room temperature. Aqueous NaHCO₃ (50%) was added (25 mL), and the organic layer was extracted
35 with CH₂Cl₂ (2 x 25 mL), dried over Na₂SO₄, filtered and evaporated. The colorless oil which remained was

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identified as the desired ester (16), (1.19 g, 7.64 mmol, 98%).

¹H NMR: 5.83 (m, 1 H, H-6), 4.96 (m, 2 H, H-7), 4.15
5 (q, 2 H, q, J = 7 Hz, OCH₂CH₃), 2.36 (t, J = 7.2 Hz, 2 H, H-2), 2.05 (q, J = 8 Hz, 2 H, H-5), 1.61 (m, 2 H, H-3), 1.45 (m, 2 H, H-4), 1.33 (t, 3 H, J = 7 Hz, OCH₂CH₃).

¹³C NMR: 173.34 (C-1), 138.01 (C-6), 114.32 (C-7),
10 58.83 (OCH₂CH₃), 33.82 (C-2), 33.01 (C-5), 28.02 (C-3), 24.14 (C-4), 13.72 (OCH₂CH₃).

6-Hepten-1-ol (17):

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A solution of the ester (16), (0.6 g, 3.85 mmol) in THF (5 mL) was cooled to 0°C in an ice/salt bath. A solution of DIBAL (1 M in Hexane, 6 mL, 6 mmol) was added dropwise with stirring over 10 min. The solution was
20 then warmed to ambient temperature and allowed to stir for an additional 2 h. The excess DIBAL was carefully quenched by the addition of 10 mL of H₂O. The organic layer was extracted with CHCl₃ (2 x 15 mL), combined, and dried over Na₂SO₄. Evaporation of the solvent,
25 chromatography on silica gel (93:7 CHCl₃/MeOH) gave the alcohol (17) as a colorless oil (0.4 g, 3.54 mmol, 92%).

¹H NMR: 5.85 (m, 1 H, H-6), 4.95 (m, 2 H, H-7), 3.62
30 (t, 2 H, J = 6 Hz, H-1), 2.62 (bs, 1 H, OH), 2.02 (m, 2 H, H-2), 1.54 (m, 2 H, H-5), 1.55 (m, 4 H, H-3, H-4).

¹³C NMR: 138.76 (C-6), 114.24 (C-7), 62.5 (C-1),
33.62 (C-2), 32.47 (C-5), 28.60 (*C-3), 25.11 (*C-4).

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* Assignments for C₃ and C₄ may be interchanged.

N-(5,5-Diacetoxypentyl) doxorubicin hydrochloride

(2a):

A stirred solution of doxorubicin hydrochloride (20 mg, 0.035 mmol) and 5-pentanal-1,1-diacetate (10) (14 mg, 2 eq, 0.07 mmol) in CH₃CN-H₂O (2:1) (5 mL) was treated with a solution of NaBH₃CN (1M in THF) (24 uL, 0.67 eq, 0.024 mmol). The mixture was stirred under a nitrogen atmosphere at room temperature in the dark for 1 h. When reaction was complete (as evidenced by TLC of a 5 uL aliquot) the solution was diluted with H₂O (8 ml) and then extracted repeatedly (10 x 10 mL) with CHCl₃-MeOH (5:1). The combined extracts were dried and evaporated to give a red amorphous solid (16 mg). Preparative TLC of this product (,CHCl₃-MeOH, 10:1; R_f = 0.60) afforded N-(pentan-5-al diacetoxyl acetal) doxorubicin (10 mg, 0.0137 mmol). The product was suspended in H₂O (1 mL) and acidified to pH 5 by dropwise addition of 0.05 N HCl (approx. 0.5 mL). The solution was lyophilized to afford the title compound (10.25 mg ,0.0134 mmol, 38%). It was then stored under a nitrogen atmosphere in a tightly stoppered vessel at -78°C in the dark.

¹H NMR (free base) : 8.01 (dd, J = 8.2, 0.9 Hz, 1 H, H-1), 7.82 (t, J = 8.2 Hz, 1 H, H-2), 7.39 (dd, J = 8.2, 0.9 Hz, 1 H, H-3), 6.73 (t, J = 5.46, 1 H, H-5"), 5.52 (t, J = 1 Hz, 1 H, H-1'), 5.3 (bs, 1 H, H-7), 4.75 (s, 2 H, H-14), 4.12 (s, 3 H, CH_{3ac.}), 3.62 (bs, 1 H, H-5'), 3.62 (m, 1 H, H-4'), 3.25 (d, J = 16 Hz, 1 H, H-10a), 2.95 (d, J = 16 Hz, 1 H, H-10b), 2.85 (m, 1 H, H-3'), 2.65 (m, 2 H, H-1"), 2.35 (m, 1 H, H-8a), 2.25 (m, 1 H, H-8b), 2.01 (s, 6 H, CH_{3ac.}), 1.82 (m, 2 H, H-2'a), 1.76 (m, 2 H, H-4"), 1.75 (m, 1 H, H-2'b), 1.40 (m, 2 H, H-3"), 1.35 (d, J = 6 Hz, 3 H, H-6').

MS (electrospray): 730 (M + H)⁺.

N-(2,2-Diacetoxyethoxyethyl) doxorubicin HCl (2b):

The compound was prepared from doxorubicin HCl (20 mg, 0.035 mmol, O-(2,2-diacetoxyethyl)glycolaldehyde (35) (14.3 mg, 2 eq., 0.07 mmol), NaBH₃CN (1 M in THF) (24 ul, 0.67 eq, 0.024 mmol) in CH₃CN-H₂O (2:1) (5 mL), as described for (2a). When reaction was complete (as evidenced by TLC of a 5 uL aliquot) the solution was diluted with H₂O (8 ml) and then extracted repeatedly (10 x 10 mL) with CHCl₃-MeOH (5:1). The combined extracts were dried and evaporated to give a red amorphous solid (17.5 mg). Preparative TLC of this product (CHCl₃-MeOH, 10:1; R_f = 0.6) afforded N-(2,2-diacetoxyethoxyethyl) doxorubicin (9.1 mg, 0.012 mmol). The product was suspended in H₂O (1 mL) and acidified to pH 5 by dropwise addition of 0.05 N HCl (approx. 0.5 mL). The solution was lyophilized to afford the title compound (9.4 mg, 0.012 mmol, 34%). It was then stored under a nitrogen atmosphere in a tightly stoppered vessel at -78°C in the dark.

MS- electrospray : 746 (M + Me +1).

¹H NMR (free base) : 8.11 (dd, J = 8.2, 0.8 Hz, 1 H, H-1), 7.82 (t, J = 8.2 Hz, 1 H, H-2), 7.35 (dd, J = 8.2, 0.8 Hz, 1 H, H-3), 6.75 (t, 1 H, J = 5.5, H-1b") 5.50 (t, J = 1 Hz, 1 H, H-1'), 5.35 (bs, 1 H, H-7), 4.75 (s, 2 H, H-14), 4.11 (s, 3 H, CH_{3ac.}), 3.84 (bs, 1 H, H-5'), 3.77 (m, 1 H, H-4'), 3.65 (m, 2 H, H-2"a), 3.54 (m, 2 H, H-2b"), 3.25 (d, J = 16 Hz, 1 H, H-10a), 3.21 (m, 1 H, H-3'), 3.14 (m, 2 H, H-1"), 2.95 (d, J = 16 Hz, 1 H, H-10b), 2.35 (m, 1 H, H-8a), 2.25 (m, 1 H, H-8b), 2.24 (m, 2 H, H-2'a), 2.12 (m, 1 H, H-2'b), 2.01 (s, 6 H, CH_{3ac.}), 1.34 (d, J = 6 Hz, 3 H, H-6').

-30-

N-(4,4-Diacetoxybutyl) doxorubicin HCl (2c):

The compound was prepared from doxorubicin. HCl (20 mg, 0.035 mmol), 4-butanal-1,1-diacetate (15) (13.2 mg, 2 eq., 0.07 mmol) and NaBH₃CN (1 M in THF) (24 μ l, 0.67 eq., 0.024 mmol) in CH₃CN-H₂O (2:1) (5 mL) as described for (2a). When reaction was complete (as evidenced by TLC of a 5 μ l aliquot) the solution was diluted with H₂O (8 ml) and then extracted repeatedly (9 x 10 mL) with CHCl₃-MeOH (5:1). The combined extracts were dried and evaporated to give a red amorphous solid (15 mg). Preparative TLC of this product (CHCl₃-MeOH, 10:1; R_f = 0.59) afforded (4,4-diacetoxybutyl) doxorubicin (10 mg, 0.014 mmol). The product was suspended in H₂O (1 mL) and acidified to pH 5 by dropwise addition of 0.05 N HCl (approx. 0.5 mL). The solution was lyophilized to afford the title compound (10.17 mg, 0.0135 mmol, 39%). It was then stored under a nitrogen atmosphere in a tightly stoppered vessel at -78°C in the dark.

20

¹H NMR (free base) : 8.05 (dd, J = 8.1, 0.85 Hz, 1 H, H-1), 7.90 (t, J = 8.1 Hz, 1 H, H-2), 7.42 (dd, J = 8.1, 0.85 Hz, 1 H, H-3), 6.75 (t, J = 5.45 Hz, 1 H, H-4"), 5.52 (bs, 1 H, H-1'), 5.31 (bs, 1 H, H-7), 4.72 (s, 2 H, H-14), 4.05 (s, 3 H, CH_{3ac.}), 3.65 (bs, 1 H, H-5'), 3.61 (m, 1 H, H-4'), 3.32 (d, J = 16.2 Hz, 1 H, H-10a), 3.03 (d, J = 16.2 Hz, 1 H, H-10b), 2.81 (m, 1 H, H-3'), 2.60 (m, 2 H, H-1"), 2.44 (m, 1 H, H-8a), 2.22 (m, 1 H, H-8b), 2.02 (s, 6 H, CH_{3ac.}), 1.75 (m, 2 H, H-2'a), 1.75 (m, 2 H, H-3"), 1.71 (m, 1 H, H-2'b), 1.42 (m, 2 H, H-2"), 1.35 (d, J = 6 Hz, 3 H, H-6').

30

N-(6,6-Diacetoxyhexyl) doxorubicin hydrochloride**(2d):**

A stirred solution of doxorubicin hydrochloride (20 mg, 0.035 mmol) and 6-hexanal-1,1-diacetate (20) (15 mg, 2 eq, 0.07 mmol) in CH₃CN-H₂O (2:1) (5 mL) was treated with a solution of NaBH₃CN (1M in THF) (24 uL, 0.67 eq, 0.024 mmol). The mixture was stirred under a nitrogen atmosphere at room temperature in the dark for 1 hour. When reaction was complete (as evidenced by TLC of a 5 uL aliquot) the solution was diluted with H₂O (8 ml) and then extracted repeatedly (10 x 10 mL) with CHCl₃-MeOH (5:1). The combined extracts were dried and evaporated to give a red amorphous solid (18 mg). Preparative TLC of this product (CHCl₃-MeOH, 10:1; R_f = 0.60) afforded N-(6,6-diacetoxyhexyl) doxorubicin (10.4 mg, 0.014 mmol). The product was suspended in H₂O (1 mL) and acidified to pH 5 by dropwise addition of 0.05 N HCl (approx. 0.5 mL). The solution was lyophilized to afford the title compound (10.75 mg, 0.0138 mmol, 39%). It was then stored under a nitrogen atmosphere in a tightly stoppered vessel at -78°C in the dark.

¹H NMR (free base) : 8.03 (dd, J = 8.2, 0.9 Hz, 1 H, H-1), 7.84 (t, J = 8.2 Hz, 1 H, H-2), 7.37 (dd, J = 8.2, 0.9 Hz, 1 H, H-3), 6.76 (t, J = 5.46, 1 H, H-6"), 5.52 (t, J = 1 Hz, 1 H, H-1'), 5.4 (bs, 1 H, H-7), 4.75 (s, 2 H, H-14), 4.14 (s, 3 H, CH_{3ac.}), 3.65 (bs, 1 H, H-5'), 3.63 (m, 1 H, H-4'), 3.25 (d, J = 16 Hz, 1 H, H-10a), 2.96 (d, J = 16 Hz, 1 H, H-10b), 2.85 (m, 1 H, H-3'), 2.66 (m, 2 H, H-1"), 2.36 (m, 1 H, H-8a), 2.23 (m, 1 H, H-8b), 2.05 (s, 6 H, CH_{3ac.}), 1.82 (m, 2 H, H-2'a), 1.78 (m, 2 H, H-5"), 1.75 (m, 1 H, H-2'b), 1.65 (m, 2 H, H-2"), 1.40 (m, 2 H, H-3"), 1.39 (m, 2 H, H-4"), 1.32 (d, J = 6 Hz, 3 H, H-6').

N-(4,4-Diacetoxy-3,3-dimethylbutyl) doxorubicin HCl
(2e):

The compound was prepared from doxorubicin HCl (20
5 mg, 0.035 mmol), dimethyl 2,2-dimethyl-4-butanal-1,1-
diacetate (30) (15 mg, 2 eq., 0.07 mmol) and NaBH₃CN (1 M
in THF) (24 uL, 0.67 eq., 0.024 mmol), in CH₃CN-H₂O (2:1)
(5 mL), as described for (2a). When reaction was
complete (as evidenced by TLC of a 5 uL aliquot) the
10 solution was diluted with H₂O (8 ml) and then extracted
repeatedly (9 x 10 mL) with CHCl₃-MeOH (5:1). The
combined extracts were dried and evaporated to give a red
amorphous solid (17 mg). Preparative TLC of this product
(CHCl₃-MeOH, 10:1; R_f = 0.54) afforded N-(4,4-diacetoxy-
15 3,3-dimethylbutyl) doxorubicin (11.2 mg, 0.015 mmol).
The product was suspended in H₂O (1 mL) and acidified to
pH 5 by dropwise addition of 0.05 N HCl (approx. 0.5 mL).
The solution was lyophilized to afford the title compound
(10.8 mg, 0.0138 mmol, 39%). It was then stored under a
20 nitrogen atmosphere in a tightly stoppered vessel at -
78°C in the dark.

¹H NMR (free base) : 8.02 (dd, J = 8.15, 0.83 Hz, 1
H, H-1), 7.91 (t, J = 8.15 Hz, 1 H, H-2), 7.54 (dd, J =
25 8.15, 0.83 Hz, 1 H, H-3), 6.65 (s, 1 H, H-4"), 5.52 (bs,
1 H, H-1'), 5.35 (bs, 1 H, H-7), 4.72 (s, 2 H, H-14),
4.03 (s, 3 H, CH_{3ac.}), 3.65 (bs, 1 H, H-5'), 3.60 (m, 1 H,
H-4'), 3.35 (d, J = 16.4 Hz, 1 H, H-10a), 3.05 (d, J =
16.4 Hz, 1 H, H-10b), 2.95 (m, 1 H, H-3'), 2.61 (m, 2 H,
30 H-1"), 2.40 (m, 1 H, H-8a), 2.26 (m, 1 H, H-8b), 2.01 (s,
6 H, CH_{3ac.}), 1.78 (m, 2 H, H-2'a), 1.73 (m, 1 H, H-2'b),
1.55 (s, 6 H, CH₃), 1.52 (m, 2 H, H-2"), 1.35 (d, J = 6
Hz, 3 H, H-6').

N-(3,3-Diacetoxypropyloxy-1-ethyl) doxorubicin HCl

(2f):

The compound was prepared from doxorubicin HCl (20
5 mg, 0.035 mmol, 3,3-diacetatepropyloxy-1-ethanal (27)
(15.2 mg, 2 eq., 0.07 mmol), NaBH₃CN (1 M in THF) (24 ul,
0.67 eq, 0.024 mmol) in CH₃CN-H₂O (2:1) (5 mL), as
described for (2a). When reaction was complete (as
evidenced by TLC of a 5 uL aliquot) the solution was
10 diluted with H₂O (8 ml) and then extracted repeatedly (10
x 10 mL) with CHCl₃-MeOH (5:1). The combined extracts
were dried and evaporated to give a red amorphous solid
(17.5 mg). Preparative TLC of this product (CHCl₃-MeOH,
10:1; R_f = 0.6) afforded N-(3,3-diacetoxypropyloxyethyl)
15 doxorubicin (9.1 mg, 0.012 mmol). The product was
suspended in H₂O (1 mL) and acidified to pH 5 by dropwise
addition of 0.05 N HCl (approx. 0.5 mL). The solution
was lyophilized to afford the title compound (9.4 mg,
0.012 mmol, 34%). It was then stored under a nitrogen
20 atmosphere in a tightly stoppered vessel at -78°C in the
dark.

¹H NMR (free base) : 8.10 (dd, J = 8.1, 0.8 Hz, 1 H,
H-1), 7.82 (t, J = 8.1 Hz, 1 H, H-2), 7.34 (dd, J = 8.1,
25 0.8 Hz, 1 H, H-3), 6.73 (t, J = 5.4 Hz, 1 H, H-1''c) 5.52
(t, J = 1 Hz, 1 H, H-1'), 5.4 (bs, 1 H, H-7), 4.73 (s, 2
H, H-14), 4.12 (s, 3 H, CH_{3ac.}), 3.82 (bs, 1 H, H-5'), 3.75
(m, 1 H, H-4'), 3.62 (m, 2 H, H-2''a), 3.53 (m, 2 H, H-
2b''), 3.25 (d, J = 16 Hz, 1 H, H-10a), 3.20 (m, 1 H, H-
30 3'), 3.15 (m, 2 H, H-1''a), 2.95 (d, J = 16 Hz, 1 H, H-
10b), 2.38 (m, 1 H, H-8a), 2.35 (m, 1 H, H-8b), 2.24 (m,
2 H, H-2'a), 2.15 (m, 1 H, H-2'b), 2.02 (s, 6 H, CH_{3ac.}),
1.95 (dt, 2 H, J = 5.4, 2 Hz, H-2''b), 1.35 (d, J = 6 Hz,
35 3 H, H-6').

N-(8,8-Diacetoxyoctyl) doxorubicin hydrochloride

(2g):

A stirred solution of doxorubicin hydrochloride (20
5 mg, 0.035 mmol) and 8-octanal-1, 1-diacetate (24) (17.1
mg, 2 eq, 0.07 mmol) in CH₃CN-H₂O (2:1) (5 mL) was treated
with a solution of NaBH₃CN (1M in THF) (24 uL, 0.67 eq,
0.024 mmol). The mixture was stirred under a nitrogen
atmosphere at room temperature in the dark for 1 hour.
10 When reaction was complete (as evidenced by TLC of a 5 uL
aliquot) the solution was diluted with H₂O (8 ml) and then
extracted repeatedly (10 x 10 mL) with CHCl₃-MeOH (5:1).
The combined extracts were dried and evaporated to give a
red amorphous solid (19 mg). Preparative TLC of this
15 product (CHCl₃-MeOH, 10:1; R_f = 0.60) afforded N-(8,8-
diacetoxyoctyl) doxorubicin (11.6 mg, 0.015 mmol). The
product was suspended in H₂O (1 mL) and acidified to pH 5
by dropwise addition of 0.05 N HCl (approx. 0.5 mL). The
solution was lyophilized to afford the title compound
20 (11.72 mg, 0.0145 mmol, 41%). It was then stored under a
nitrogen atmosphere in a tightly stoppered vessel at -
78°C in the dark.

¹H NMR (free base) : 8.05 (dd, J = 8.2, 0.9 Hz, 1 H, H-1),
25 7.85 (t, J = 8.2 Hz, 1 H, H-2), 7.40 (dd, J = 8.2, 0.9
Hz, 1 H, H-3), 6.72 (t, J = 5.46, 1 H, H-8"), 5.55 (T, J
= 1 Hz, 1 H, H-1'), 5.35 (bs, 1 H, H-7), 4.71 (s, 2 H, H-
14), 4.16 (s, 3 H, CH_{3ac.}), 3.68 (bs, 1 H, H-5'), 3.65 (m,
1 H, H-4'), 3.28 (d, J = 16 Hz, 1 H, H-10a), 2.98 (d, J =
30 16 Hz, 1 H, H-10b), 2.85 (m, 1 H, H-3'), 2.68 (m, 2 H, H-
1"), 2.35 (m, 1 H, H-8a), 2.25 (m, 1 H, H-8b), 2.04 (s, 6
H, CH_{3ac.}), 1.85 (m, 2 H, H-2'a), 1.75 (m, 2 H, H-7"), 1.76
(m, 1 H, H-2'b), 1.68 (m, 2 H, H-2"), 1.41 (m, 2 H, H-
3"), 1.40 (m, 6 H, H-4", H-5"), 1.39 (m, 2 H, H-6"), 1.35
35 (d, J = 6 Hz, 3 H, H-6').

By usage of analogous congeners, those of skill in the art may readily adopt the above synthetic methods to produce almost innumerable varieties of the subject compounds.

5

The following references as well as those listed in the body of the specification are incorporated in pertinent part herein for the reasons cited.

10

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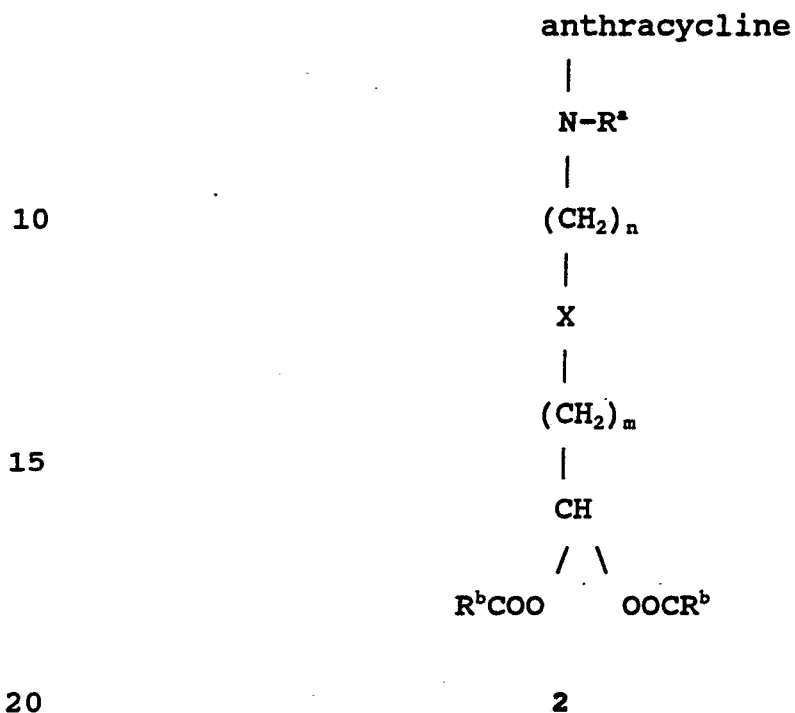
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- 35 18. Alfrebro Inc., 1055 Reed Road, Monroe, OH 45050.

CLAIMS:

1. A compound of the formula

5



where:

25 anthracycline is doxorubicin, daunorubicin or a derivative thereof;

N is the 3' nitrogen of daunosamine;

R^a is H or alkyl;

X is O, S, CR^c₂ or NR^c, where R^c is H or alkyl;

30 R^b is alkyl or aryl;

n is 1 to 6; and

m is 0 to 6.

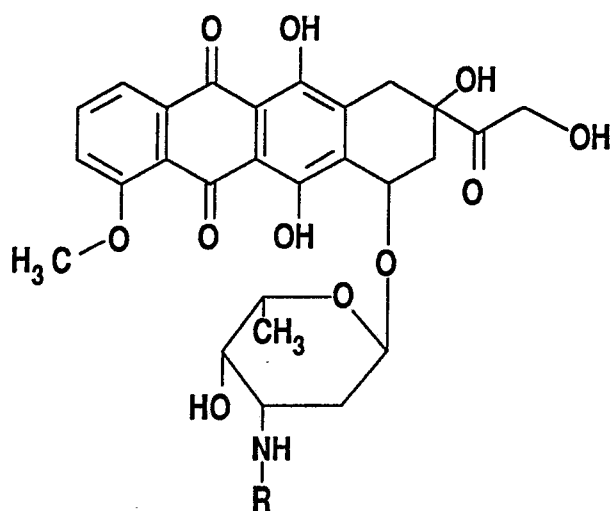
35 2. The compound of claim 1 wherein R^c is H, methyl, ethyl, propyl or butyl.

3. The compound of claim 1 wherein R^a is H, R^b is CH_3 , X is CR^c_2 , R^c is H, n is 2 and m is 1.
- 5
4. The compound of claim 1 wherein R^a is CH_3 or H, R^b is CH_3 , X is O, n is 2, and m is 1.
- 10
5. The compound of claim 1 wherein R^a is H, R^b is CH_3 , X is CR^c_2 , R^c is H, n is 2 and m is 0.
- 15
6. The compound of claim 1 wherein R^a is H, R^b is CH_3 , X is CR^c_2 , R^c is H, n is 2 and m is 2.
- 20
7. The compound of claim 1 wherein R^a is H, R^b is CH_3 , X is CR^c_2 , R^c is H, n is 2 and m is 0.
- 25
8. The compound of claim 1 wherein R^a is H, R^b is CH_3 , X is O, n is 2 and m is 2.
- 30
9. The compound of claim 1 wherein R^a is H, R^b is CH_3 , X is CR^c_2 , R^c is H, n is 2 and m is 4.
- 35
10. The compound of claim 1 wherein R^a is H, methyl, ethyl, propyl or butyl.
11. The compound of claim 1 wherein R^b is alkyl.

12. The compound of claim 1 wherein R^b is the alkyl methyl, ethyl, propyl or butyl.
- 5
13. The compound of claim 1 wherein R^b is methyl.
14. The compound of claim 1 wherein X is CR^c_2 , R^c is H,
10 and $m + n$ is from 1 to 9.
15. The compound of claim 1 wherein X is O, S or NR^c , R^c is H.
- 15
16. The compound of claim 1 wherein anthracycline is doxorubicin.
- 20
17. N-(5,5-Diacetoxypentyl) doxorubicin or a pharmaceutically acceptable salt thereof.
- 25
18. N-(2,2-Diacetoxyethoxyethyl) doxorubicin or a pharmaceutically acceptable salt thereof.
- 30
19. N-(4,4-Diacetoxybutyl) doxorubicin or a pharmaceutically acceptable salt thereof.
20. N-(6,6-Diacetoxyhexyl) doxorubicin or a pharmaceutically acceptable salt thereof.
- 35

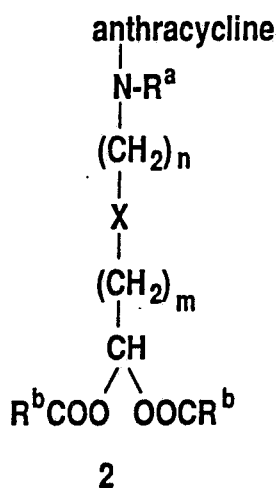
21. N-(4,4-Diacetoxy-3,3-dimethylbutyl) doxorubicin or a pharmaceutically acceptable salt thereof.
- 5 22. N-(3,3-Diacetoxypropyloxy-1-ethyl) doxorubicin or a pharmaceutically acceptable salt thereof.
- 10 23. N-(8,8-Diacetoxyoctyl) doxorubicin or a pharmaceutically acceptable salt thereof.

1/2



- a, R = $\text{NHCOC}_6\text{H}_4(\text{p})\text{SO}_2\text{F}$
 b, R = NHCOCH_2Br
 c, R = NHCOCH_2Cl
 d, R = $\text{NHCON}(\text{NO})\text{CH}_2\text{CH}_2\text{Cl}$

Fig. 1



where:

anthracycline is doxorubicin, daunorubicin or a derivative thereof;

N is the 3' nitrogen of daunosamine

R^a is H or alkyl;

X is O, S, CR_2^c or NR^c where R^c is H or alkyl;

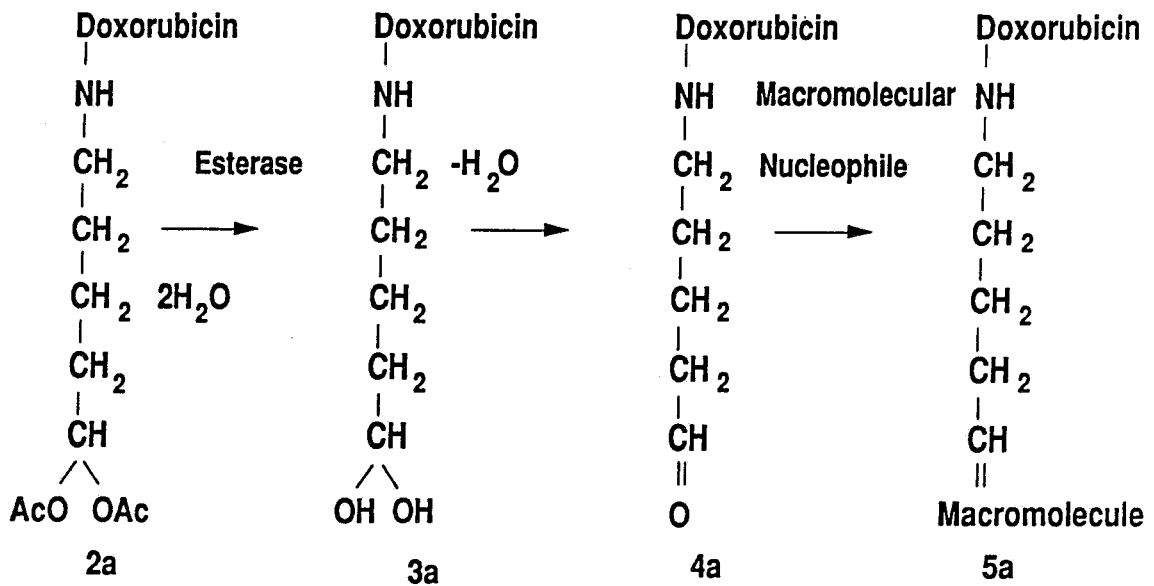
R^b is alkyl or aryl;

n is 1 to 6; and

m is 0 to 6.

Fig. 2

2/2



Where Doxorubicin is the N^{3'}-substituted doxorubicin residue, and Macromolecule represents a cellular macromolecule.

Fig. 3

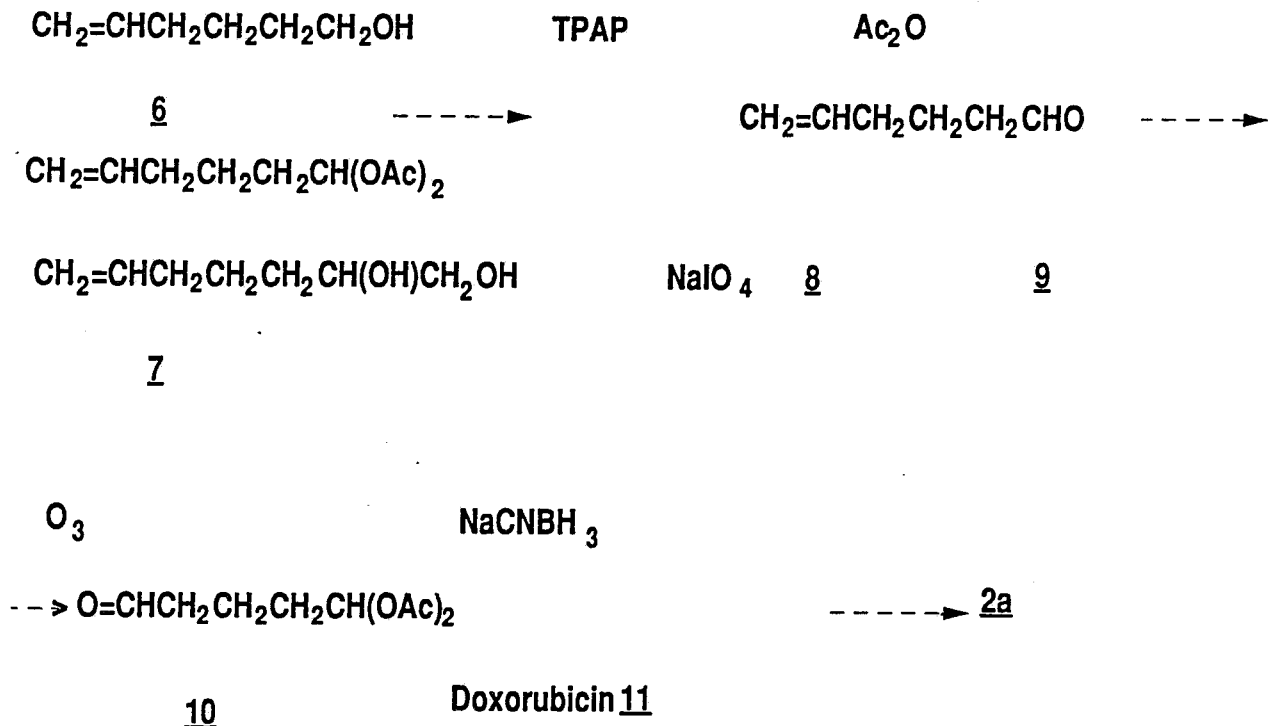


Fig. 4

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 91/07687

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC Int.Cl. 5 C07H15/252; A61K31/70		
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl. 5	C07H ; A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	WO,A,9 010 636 (BOARD OF REGENTS, THE UNIVERSITY OF TEXAS SYSTEM) 20 September 1990 cited in the application see example 8 ---	1-23
A	EP,A,0 226 173 (BEHRINGWERKE AKTIENGESELLSCHAFT) 24 June 1987 see claims ---	1-23
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents :</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report	
12 MARCH 1992	20. 03. 92	
International Searching Authority	Signature of Authorized Officer	
EUROPEAN PATENT OFFICE	DAY G. J.	

3

**ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.**

US 9107687
SA 53560

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 12/03/92

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9010636	20-09-90	AU-A- 3447189	09-10-90
		US-A- 5055459	08-10-91
EP-A-0226173	24-06-87	FR-A- 2591599	19-06-87
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