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54. TÍTULO PROCESO PARA LA SINTESIS DE
ANTRACICLINAS OPTICAMENTE ACTIVAS

51. CLASIFICACIÓN INTERNACIONAL AGIX³¹/015, CO7H¹⁵/25

71. SOLICITANTE MENARINI RICERCHE S.P.A.

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1

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Patente de Invención

Patente de Modelo de Utilidad

Capítulo I.

X

Capítulo II.

2

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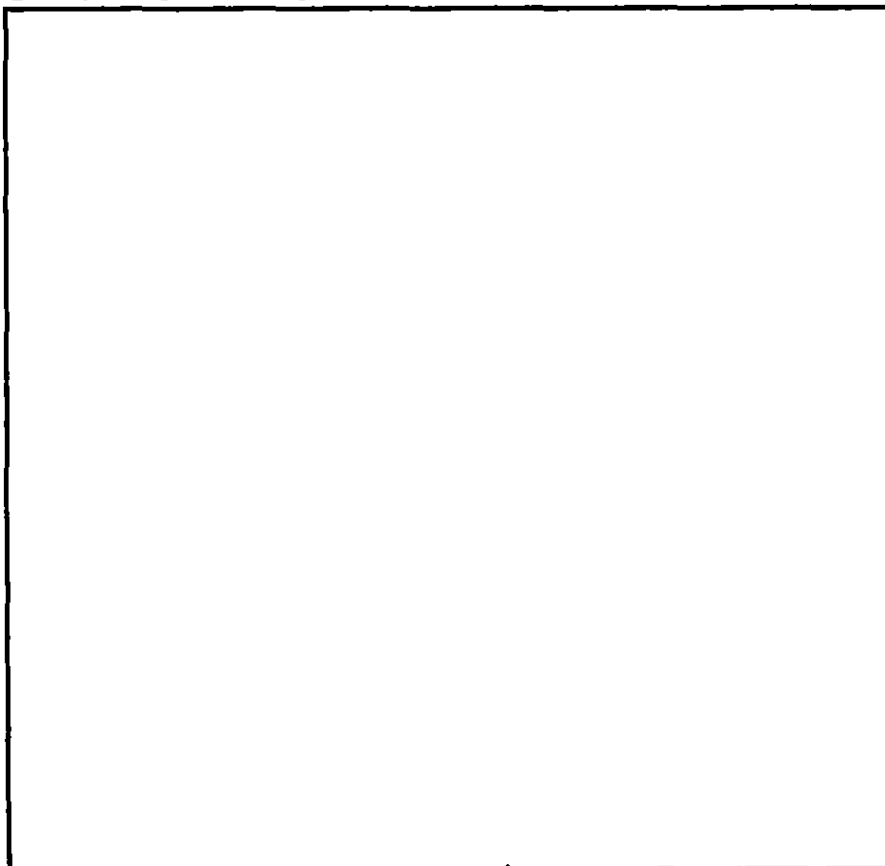
ANEX S

2

- ☒ Comprobante de pago de la tasa de presentación de la solicitud \$400.000.00
- ☒ Comprobante de pago por reivindicación de prioridad \$112.000.00
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona jurídica
- ☒ Poderes, si fuere el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Traducción de la solicitud internacional al castellano (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA)
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- ☐ De ser el caso, modificaciones efectuadas a la solicitud internacional
- ☐ Otros

11

FIGURA CARACTERÍSTICA:



12

Solicito la concesión de la patente,

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FIRMA:

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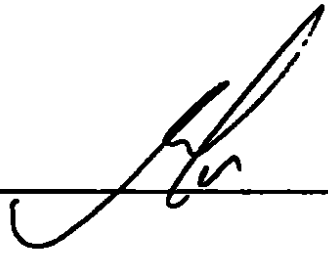
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DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
ALIRIO GOMEZ LOBO	CONSIGNACION	BANCO POPULAR	050-00110-6	15534505	23/04/2003	112,000.00
ALIRIO GOMEZ LOBO	CONSIGNACION	BANCO POPULAR	030-00110-6	15534506	23/04/2003	400,000.00

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CANT. HISTORICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	400,000.00
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***** C O N S I G N A C I O N *****

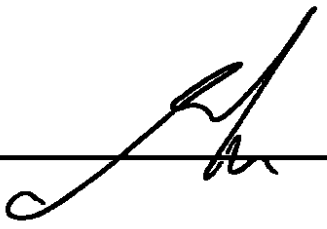
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ALIRIO GOMEZ LOBO	CONSIGNACION	BANCO POPULAR	050-00110-6	15534505	23/04/2003	112,000.00
ALIRIO GOMEZ LOBO	CONSIGNACION	BANCO POPULAR	030-00110-6	15534506	23/04/2003	400,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	82 INVOCACION DE UNA PRIORIDAD EN NU	112,000.00
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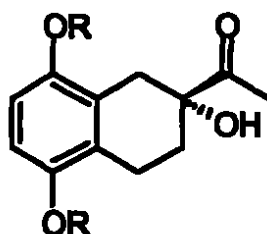
(54) Title: PROCESS FOR THE SYNTHESIS OF OPTICALLY ACTIVE ANTHRACYCLINES

(57) Abstract: It is described a process for the synthesis of optically active anthracyclines characterised by the fact that the key intermediate (R)2-acetyl-2-hydroxy-1,2,3,4-tetrahydronaphthalene 5,8-dialkoxy is prepared from 5,8-dialkoxy-3,4-dihydronaphthalene by acylation asymmetric dihydroxylation, transformation into chloroacetate, dehydrochloridation and final hydrolysis.

PROCESS FOR THE SYNTHESIS OF OPTICALLY ACTIVE ANTHRACYCLINES

Field of the invention

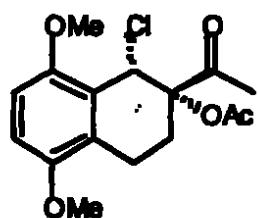
The present invention refers to a process for the synthesis of optically active anthracyclines wherein the optically active key intermediate (R) 2-acetyl-2-hydroxy-1,2,3,4-tetrahydronaphthalene 5,8-dialkoxy of formula I.



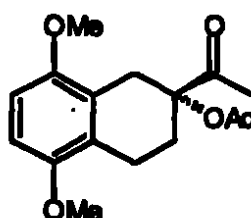
wherein: R = C₁₋₃ alkyl, preferably methyl.

is prepared starting from 5,8-dialkoxy-3,4-dihydronaphthalene by acylation, asymmetric dihydroxylation, transformation into chloroacetate dehydrochloridation and final hydrolysis.

The invention refers also to the intermediates of formula V e VI:



V

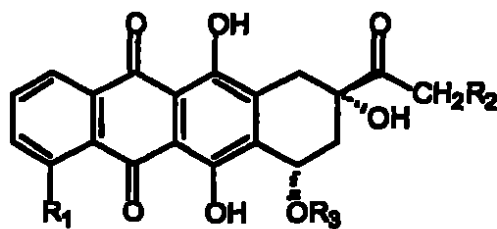


VI

Having an enantiomeric excess higher than 95%.

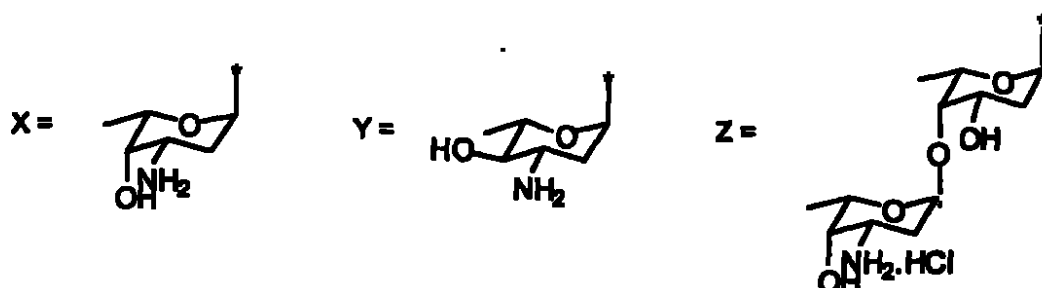
State of the art

As it is known the anthracyclines of formula VIII



VIII

Wherein: R₁ = H, OH, OCH₃; R₂ = H, OH; R₃ = X, Y or Z where



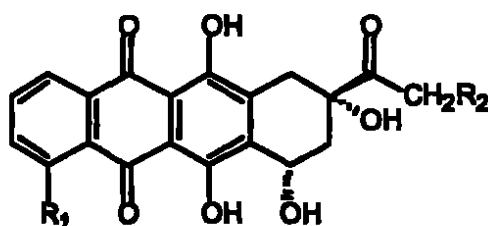
are compounds having a wide therapeutic use as anti-neoplastic drugs.

Known compounds of formula VIII having the above said properties are for
 5 example Daunomicin (VIII, wherein: $R_1 = \text{OCH}_3$, $R_2 = \text{H}$, $R_3 = \text{X}$), Doxorubicin
 (VIII wherein: $R_1 = \text{OCH}_3$, $R_2 = \text{OH}$, $R_3 = \text{X}$), Epirubicin (VIII wherein: $R_1 = \text{H}$,
 $R_2 = \text{H}$, $R_3 = \text{X}$) e Epirubicin (VIII wherein: $R_1 = \text{OCH}_3$, $R_2 = \text{OH}$, $R_3 = \text{Y}$), or the
 compounds described in EP721456, in particular the compound of formula VIII
 wherein $R_1 = \text{H}$, $R_2 = \text{OH}$, $R_3 = \text{Z}$, disaccharide anthracycline which is now under
 10 clinical development.

The synthesis of anthracycline of formula VIII requires many steps and is normally
 performed starting from an optically active tetraline of formula I which is reacted by
 a Friedel-Crafts reaction with phthalic anhydride or its derivatives as phthaloyl
 dichloride or phthaloyl chloride methylester and thereafter cyclised. The so
 15 obtained tetracycline is protected in the 13-oxo position with ethyleneglycol, is
 brominated in position 7 and converted into a 7-OH derivative with known methods
 (see Arcamone et al. , *Experientia*, 1978, 34, 1255; Wong et al. *Can. J. Chem.*,
 1971, 49, 2712; Swenton et al. , *Tetrahedron*, 1984, 40, 4625). After deprotection
 the anthracycline of formula VII (wherein $R_2 = \text{H}$) is used as such or is converted
 20 into a 14 acyloxy derivative (compound of formula VII wherein $R_2 = \text{O-acyl}$) according to known procedures.. Thereafter the compounds of formula VII are
 glycosidated with protected mono- or disaccharides as described in literature (see
 Arcamone et al., *Experientia*, 1978, 34, 1255; Terashima et al., *Bull. Chem. Soc.*
Jpn, 1986, 59, 423) and in EP 6, by deprotection the anthracycline of formula
 25 VIII are obtained.

In the above described process, or in other similar processes which include as
 intermediate a tetraline, the key intermediate is the tetraline of formula I itself as
 above defined.

This AB synthon (Wong et al. Can. J. Chem, 1971, 49, 2712) allows the formation of the corresponding optically active anthracycline of formula VII wherein $R_1 = H, OH, OCH_3$ and $R_2 = H, OH, O\text{-acyl}$ wherein the acyl group is chosen among formyl, acetyl, mono-, di- or trichloroacetyl, preferably acetyl.



VII

As above said the compound is finally converted in the desired anthracycline.

The stereochemistry of position C-9 of the anthracycline is very important for the biological activity of these compounds since only the compounds having (S) configuration in C-9 show an antitumour activity.

Therefore also the tetraline intermediate of formula I must obviously possess the same stereochemistry (i.e. an absolute configuration R).

The tetraline I is normally prepared. According to the literature, as a racemic mixture starting from 2-acetyl-5,8-dimethoxy tetraline III by oxydilation in position C-2 with potassium t-butoxide/t-butanol in the presence of oxygen followed by reduction "in situ" (Wong et al., Can. J. Chem., 1971, 49, 2712 ; Gardner et al., J.Org. Chem.1968, 33, 3294).

The compound III was prepared, with very low yields by reacting 5,8-dimethoxy-3,4-dihydronaphthalene II with N-N-diphenylacetamide- $POCl_3$ applying the conditions of the Vilsmeier-Haack reaction followed by the reduction of the double bond.

Several attempts of acylating compound II have been reported but all unsuccessful (Rama Rao et al. Ind.J.Chem.1985, 24B, 697).

Alternatively the compound III was prepared with a yield of about 50% in 4 steps by reaction of 5,8-diacetoxy-3,4-dihydronaphthalene with acetyl chloride/ $AlCl_3$ and formation of a chloroacetyl derivative, followed by dehydrochloridation with $LiCl$, hydrolysis and methylation "in situ" (Russell et al. J. Chem. Soc. Chem. Comm. 1983, 994).

Another reaction path for obtaining the precursor III reported in literature includes five steps starting from 5,8-dihydroxy-1,4-dihydronaphthalene with a total yield of about 50% (Giles et al. S.Afr.J.Chem, 1990, 43, 87).

The racemic tetraline I is thereafter converted into the pure enantiomeric compound using the normal methods applied for the resolution of racemes through diastereoisomeric Schiff bases on the acetyl lateral chain with (-)-1-phenylethylamine (Arcamone et al. BP 02691/75, 1975). Alternatively the enantiomeric pure compound was prepared by Kinetic resolution via a Sharpless asymmetric epoxidation followed by oxidation of the obtained allyl alcohol obtained by reducing 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (Sharpless et al. J.Am.Chem.Soc. 1981, 103, 6237). Another method for obtaining the optically pure tetraline consists in the stereoselective reduction of the racemic mixture with baker's yeast to diastereoisomeric diols mixtures followed by chromatographic separation and re-oxidation (Terashima et al., Chem. Pharm. Bull. 1984, 32, 4328).

An asymmetric synthesis of the tetraline I starting from precursor III by enantioselective dihydroxylation is described in M. Nakajima et al. Tetrahedron, 1993, 49, 10807, but the several steps and the final excess of tetraline I and especially the use of osmium tetroxide in stoichiometric quantities, instead of catalytic, quantities and the use of expensive chiral amines (always in stoichiometric quantities) quantities at a temperature of - 110°C, makes very difficult the industrial use of this synthesis.

Other asymmetric synthesis of AB synthon using chiral compounds or compounds comprising chiral derivatives of natural compounds are reported in literature but all these syntheses are very complex and unsuitable for industrial application (Krohn, Angew. Chem. Int. Ed. Engl., 1988, 25, 790).

Summary of the Invention

The present invention describes a process for the preparation of anthracyclines of formula VIII as above defined VIII wherein the optically active tetraline of formula I as above defined is stereoselectively prepared starting from 5,8-dialkoxy-3,4-dihydronaphthalene II which, contrary to the methods applying the resolution of racemic mixture, which are difficult to perform, and give yields inferior to 30%,

shows the advantage of giving the key intermediate I in yields much higher than those reported in literature and is easily industrially exploitable.

In particular, although the literature reported as fruitless, or non interesting because of the low yields, the attempts of acylating compound II (Rama Rao et al. Ind.J.Chem.1985, 24B, 697, Russell et al. J. Chem. Soc. Chem. Comm. 1983, 994, Giles et al. S.Afr.J.Chem, 1990,43, 87), the 5,8-dialkoxy-3,4-dihydronaphthalene (compound of formula II wherein R is a group C₁₋₃ alkyl, preferably methyl) can surprisingly be acylated in just one step in the presence of an acyl chloride and aluminium trichloride forming the corresponding acyl derivative III. Moreover this innovative application of the procedure of enantioselective catalytic dihydroxylation of olefins (Sharpless et al., Chem. Rev. 1994, 94, 2483) to give the insature acyl derivative allows to obtain the optically active diol IV in a good yield. The compound is thereafter converted into the corresponding 1-chloro-2-acetyl-derivative by Sharpless procedure (Sharpless et al, Tetrahedron, 1992, 48, 10515) and dehalogenated following known methods, for example by catalytic hydrogenation or in the presence of tin and a radical precursor or can be directly dehydroxylated by catalytic reduction. The final hydrolysis of the ester group allows the formation of compound I in good yields and high optical purity.

Detailed description of the invention

In Schema I it is reported a process for obtaining the tetraline of formula I wherein R = CH₃. In this case the starting product is the 5,8-dimethoxy-3,4-dihydronaphthalene II, obtained by known methods starting from butadiene and p-quinone (Fieser et al., J.Am.Chem.Soc., 1948, 70, 3151).

In spite of the fact that in literature the attempts of acylating the compound II were reported as fruitless or non interesting because of the low yields, the 5,8-dimethoxy-3,4-dihydronaphthalene II is treated with acetyl chloride in the presence of an excess of aluminium trichloride, preferably 5 – 9 moles of aluminium trichloride for one mole of acyl chloride, at the temperature of -35° + 25°C, preferably at 0°C. After the usual work-up and crystallisation with ethyl acetate, the product, 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene is obtained in yields higher than 70%.

Compound III is stereoselectively converted to diol IV by a Sharpless asymmetric dihydroxylation which is described in literature for other olefin substrates (Sharpless et al., Chem. Rev. 1994, 94, 2483). The reagent used in this step is AD-mix α (catalogue Aldrich, reagent 39275-8, see also J. Org. Chem. 1992, 57, 2768) with a further addition of the osmium salt ($K_2OsO_2(OH)_4$) and methanesulphonamide.

The osmium salt is always in catalytic quantity vis-à-vis the substrate. The reaction is performed at low temperature, -4 to +20°C, preferably at 0°C, the yield is 70%, with an enantiomeric excess higher than 95%.

10 The optically active diol IV is converted into a chloroacetate V through the formation "in situ" of a cyclic intermediate using trimethylorthoacetate in the presence of an acid catalyst followed by treatment with trimethylsilyl chloride according to a method already described in literature for different diols (Sharpless et al. Tetrahedron, 1992, 48, 10515).

15 This step gives yields higher than 80%.

The reduction of the chloroacetate to acetate VI can be performed photochemically or by thermal treatment in the presence of tributyltinhydride and radical precursors as AIBN or BPO or by catalytic hydrogenation.

The yields are higher than 80%.

20 The acetate can be obtained directly by catalytic reduction of diol IV.

The hydrolysis of the acetate can be performed with ionic exchange resins in quantitative yield. Alternatively the known methods for the hydrolysis of the acetates, as the treatment with sodium methoxide or sodium hydroxide.

25 What reported in Scheme I can be easily applied to the synthesis of all the compounds of formula I, using the corresponding starting products.

The tetraline I which is an object of the present invention is therefore obtained in only 4-5 steps with a total yield much higher than the one reported for the known processes.

Moreover, the reaction conditions as described make it possible the industrial scale up of the process. The subsequent steps of the process through the anthracyclnone to the final anthracycline are performed as described in literature.

The process according to the invention will be better understood in the light of the hereinafter reported Example which refers to the Scheme 1 i.e. to the preparation of the tetraline of formula I wherein R = CH₃.

EXAMPLE 1

5 Synthesis of III

To a suspension of aluminium trichloride (449 g) in dichloromethane (2 l) in nitrogen current, acetyl chloride (380 ml) is added drop by drop at 0°C. After 30 min. stirring at 0°C, to the so obtained solution a solution of 5,8-dimethoxy-3,4-dihydronaphthalene II (80 g) in dichloromethane (2,5 l) is slowly added drop by
10 drop. After 30 min stirring at 0°C the mixture was hydrolysed with ice. After separation of the organic phase and washing with HCl 1N (3 x 6 l), H₂O (3 x 4l) and brine (2 x 4 l), the solvent was evaporated u.v. at 40°C giving a yellow solid residue (98 g). By crystallisation from refluxing ethyl acetate 71 g of the desired compound III were obtained.

15 Yield 73 %.

¹H NMR (CDCl₃): 2.44 (s, 3H, H₁₀); 2.53 (m, 2H, H₉); 2.80 (m, 2H, H₅); 3.30, 3.84 (2s, 6H, OCH₃); 6.75 (dd, 2H, H₂ + H₃); 7.81 (m, 1H, H₈);

¹³C NMR (CDCl₃): 19.9, 20.5 (C₅, C₆); 25.3 (C₁₀); 55.9, 58.1 (OCH₃); 108.5, 113.2 (C₂, C₃); 122.6, 127.2 (C_{4a}, C_{8a}); 131.5 (C₈); 137.2 (C₇); 150.4, 151.0 (C₁, C₄);
20 198.8 (C₉).

TLC: r.f. 0.80 (Petrol ether/Ethyl acetate = 80/20).

HPLC: r.t. = 8.9 min (Conditions: Lichrospher 100 RP 18 (5µm, 250 x 4 mm)
CH₃CN / H₂O + 0.1 % TFA = 60 / 40; 1 ml/min; λ = 214 nm; 20 µl of a solution 1
mg/10ml)

25 EXAMPLE 2

Synthesis of IV

To a solution of AD mix-α (600 g) and K₂OsO₂(OH)₄ (1 g) in water (2 l) t-butanol (2.15 l), methanesulphonamide (40.7 g), sodium bicarbonate (109 g) are added. The mixture was stirred up to complete solution of the solid components, cooled
30 down at 0°C, added with 4-acetyl-3,4-dihydronaphthalene (100 g) and vigorously stirred for 96 h.

After complete reaction of the precursor, checked by TLC (Petrol ether/ethyl acetate = 80/20), 630 g of sodium bisulphite are added in portions and, after 1 h stirring, 4 l of AcOEt are added and the phases are separated.

The organic phase was washed with NaOH 1N (1 x 2 l), H₂O (1 x 2 l) and
5 evaporated under vacuum.

The obtained solid was solved in 750 ml CH₂Cl₂ and the solution was extracted with H₂SO₄ 3 % saturated with K₂SO₄ (4 x 200 ml), NaHCO₃ s.s. (1 x 300 ml) and H₂O (1 x 300 ml).

The organic phase, dried on anhydrous MgSO₄, was evaporated under vacuum
10 leaving a solid residue.

The product was crystallised from AcOEt / cyclohexane = 1/1, filtered and dried under vacuum.

78.7 g of a crystalline solid were obtained. Yield: 70.5%

¹H NMR (CDCl₃): 1.87 (m, 2H, H₈); 2.38 (s, 3H, H₁₀); 2.79 (m, 2H, H₆); 3.78, 3.84
15 (2s, 6H, OCH₃); 3.81 (m, 1H, H₉); 4.87 (d, 1H, OH₈); 5.29 (s, 1H, OH₇); 6.71 (s, 2H, H₂ + H₃).

¹³C NMR (CDCl₃): 19.1 (C₁₀); 25.8 (C₈); 28.7 (C₉); 55.7, 55.7 (OCH₃); 68.5 (C₆); 78.7 (C₇); 108.0, 108.8 (C₂, C₃); 125.8, 127.1 (C_{4a}, C_{8a}); 151.1, 152.3 (C₁, C₄); 214.2 (C₅).

20 TLC: r.f. 0.25 (Petrol ether/Ethyl acetate = 80/20)

HPLC: r.t. = 4.1min (Conditions: Lichrospher 100 RP 18 (5µm) 250 x 4 mm CH₃CN / H₂O + 0.1 % TFA = 50 / 50; 1 ml/min; λ = 214 nm; 20 µl of a solution 2.8 mg/10ml)

e.e. = 98 % determined by chiral HPLC (Conditions: Chiralcel OD 250 X 4.6 mm; n-hexane / EtOH = 90 / 10; 1 ml/min; λ = 214 nm; 20 µl of a solution 1.3 mg / 10
25 ml)

m. p. = 141-143°C.

[α]_D²⁵ = -21.9° (c = 1.0, CHCl₃)

EXAMPLE 3**Synthesis of V**

To a solution of diol (77 g) in CH_2Cl_2 (600 ml), under nitrogen, trimethylorthoacetate (59.3 ml) and piridiniumtoluene-4-sulphonate (2 g) are added.

The solution is stirred at room temperature for 24 h. The solvent is evaporated under vacuum leaving a solid residue.

The solid was solubillised CH_2Cl_2 (600 ml) and added, under nitrogen, with trimethylsilyl chloride (65 ml). The reaction mixture is stirred at room temperature for 1 h and, after evaporation of the solvent under vacuum, was treated with cyclohexane (400 ml) under vigorous stirring for 3 h.

The solid was filtered and dried under vacuum.

98.1 g of the desired product were obtained (quantitative yield).

^1H NMR (CDCl_3): 1.96 (s, 3H, H_{10}); 1.97 – 3.15 (m, 4H, $\text{H}_5 + \text{H}_6$); 2.43 (s, 3H, H_{12}); 3.81, 3.87 (2s, 6H, OCH_3); 5.35 (d, 1H, H_8); 6.76 (dd, 2H, $\text{H}_2 + \text{H}_3$);

^{13}C NMR (CDCl_3): 19.6 (C_{11}); 20.2, 20.5 (C_5 , C_6); 26.3 (C_{12}); 52.9 (C_8); 55.6, 56.0 (OCH_3); 82.9 (C_7); 108.3, 110.1 (C_2 , C_3); 123.2, 125.4 (C_{4a} , C_{8a}); 150.7, 151.6 (C_1 , C_4); 169.6 (C_{11}); 204.2 (C_9).

TLC : r.f. = 0.55 (Petrol ether / AcOEt = 75 / 25)

m.p. = 128-138°C.

$[\alpha]_D^{25} = -16.2^\circ$ (c = 1.0, CH_2Cl_2).

EXAMPLE 4**Synthesis of VI**

To a solution of chloacetate (97.3 g) in toluene (2 l) AIBN (1.5 g) and tributyltinhydruce (225 ml) were added in nitrogen current. The mixture was stirred under the light of a 200 Watt wolfram lamp for 24 h and thereafter extracted with water (500 ml). The organic phase is separated, dried and evaporated under vacuum. The residue is treated with cyclohexane (500 ml) under stirring, filtered and dried under vacuum at 40°C.

67.8 g of the desired product are obtained in the form of a white solid.

Yield : 80.3 %.

¹H NMR (CDCl₃): 1.95, 2.50 (2m, 2H, H₈); 2.05 (1.3H, H₁₀); 2.22 (1.3H, H₁₂); 2.40, 2.90 (2m, 2H, H₅); 3.00 (dd, 2H, H₉); 3.77, 3.80 (2s, 6H, OCH₃); 6.66 (m, 2H, H₂ + H₃).

¹³C NMR (CDCl₃): 19.5, 21.0 (C₅, C₆); 24.0 (C₁₀); 26.7 (C₁₂); 30.2 (C₈); 55.6, 55.5 (OCH₃); 83.6 (C₇); 107.0, 107.2 (C₂, C₃); 122.7, 125.1 (C_{4a}, C_{8a}); 150.9, 151.4 (C₁, C₄); 170.5 (C₁₁); 206.5 (C₉).

TLC : r.f. = 0.28 (Toluene/Ethylacetate = 95/5)

HPLC: r.t. = 7.4 min (Conditions: Lichrospher 100 RP 18 (5μm) 250 x 4 mm, CH₃CN / H₂O + 0.1 % TFA = 60 / 40; 1 ml/min; λ = 214 nm; 20 μl of a solution 1.2

mg / 10 ml)

m.p.: 110-118°C.

[α]_D²⁵: -46.3° (c = 1.0, CHCl₃).

EXAMPLE 5

Synthesis of I

To a solution of acetate (66 g) in methanol (5 l) the Amberlite IRA-400 resin (OH) (183 ml) previously activated by treatment with NaOH 30% (8 x 400 ml) and washed with water (5 x 400 ml) and methanol (4 x 400 ml) was added. The reaction mixture is stirred for a night at room temperature. After removal of the resin by filtration and evaporation of the solvent under vacuum a solid residue was obtained which after crystallisation from cyclohexane/ethylacetate, filtration and drying gave 51.85 g of desired product.

Yield: 92 % .

¹H NMR (CDCl₃): 1.89 (m, 2H, H₈); 2.33 (s, 3H, H₁₀); 2.91 (m, 4H, H₅ + H₉); 3.65 (s, 1H, OH); 3.77, 3.80 (2s, 6H, OCH₃); 6.66 (s, 2H, H₂ + H₃).

¹³C NMR (CDCl₃): 19.2 (C₅); 23.9 (C₁₀); 29.7, 32.4 (C₆, C₈); 55.5, 55.6 (OCH₃); 76.4 (C₇); 107.0, 107.4 (C₂, C₃); 122.7, 125.5 (C_{4a}, C_{8a}); 151.1, 151.6 (C₁, C₄); 212.3 (C₉).

TLC: r.f. = 0.27 (Petrol ether/Ethylacetate = 80/20)

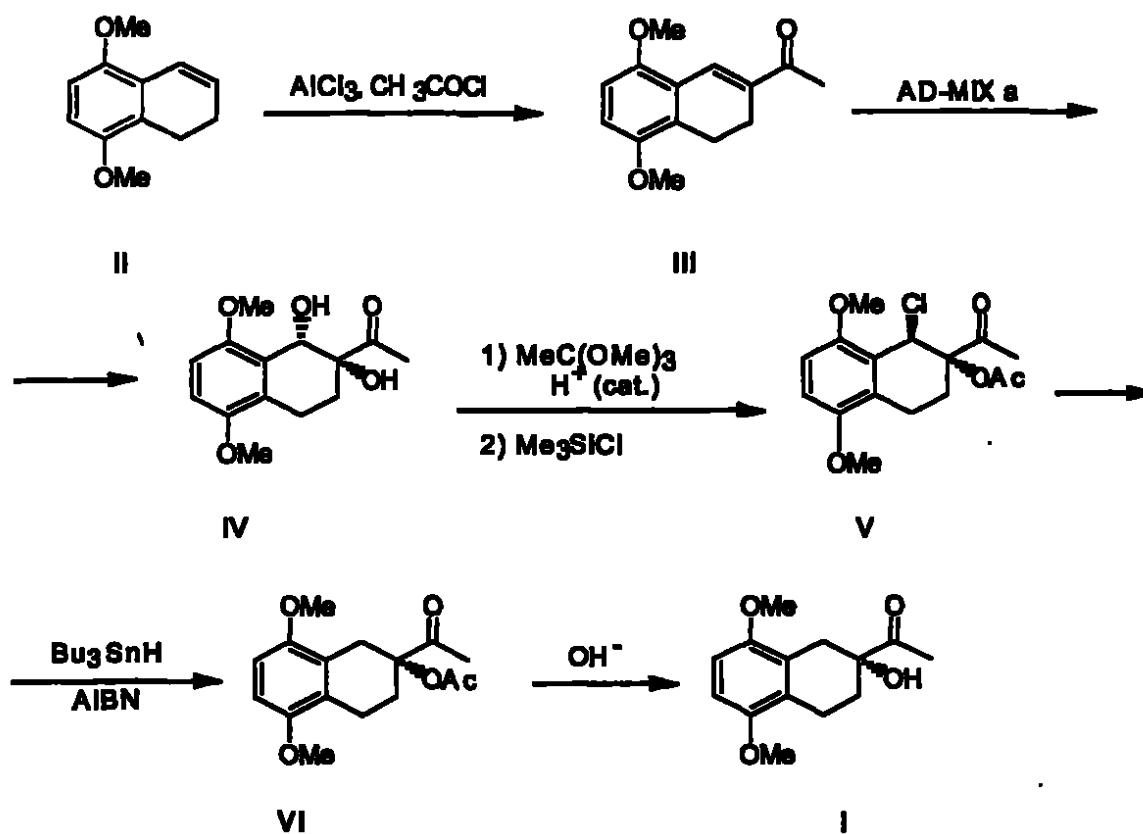
HPLC : r.t. = 5.9 min (Conditions: Lichrospher 100 RP 18 (5μm) 250 x 4 mm,

CH₃CN / H₂O + 0.1 % TFA = 50 / 50; 1 ml/min; λ = 214 nm; 20 μl of a solution 2.5 mg/ml)

e.e = > 99% determined by chiral HPLC (Conditions: Chiralcel OD 250 X 4.6 mm; *n*-hexane / EtOH = 90 / 10; 1 ml/min; λ = 214 nm; 20 μ l of a solution 1.35 mg / 10 ml)

m.p. : 126-129°C.

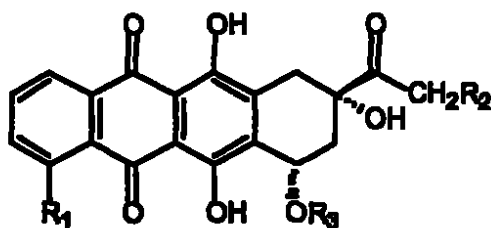
5 $[\alpha]_D^{25} = -46.2^\circ$ (c = 1.0, CHCl₃)



SCHEME I

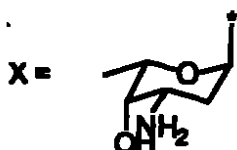
Claims

1. Process for the preparation of anthracycline of formula VIII:

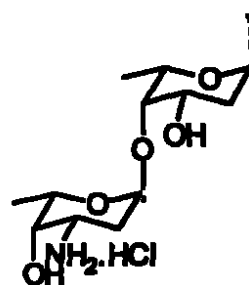


VIII

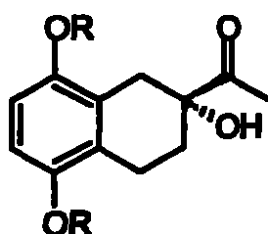
5 wherein $R_1 = \text{H, OH, OCH}_3$; $R_2 = \text{H, OH}$; $R_3 = \text{X, Y or Z}$ where:



Z =



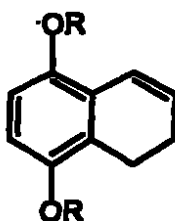
comprising the formation of the intermediate of formula (I):



I

10 wherein: $R = \text{C}_{1-3}$, alkyl

characterised in that said intermediate of formula (I) is prepared starting from a 5-dialkoxy-3,4-dihydronaphthalene of formula (II):

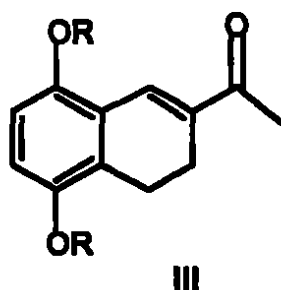


II

15 wherein $R = \text{C}_{1-3}$ alkyl

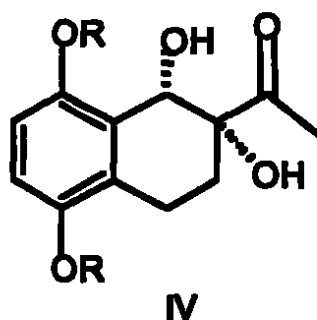
2. Process according to claim 1, wherein:

- a) the 5,8-dialkoxy-3,4-dihydronaphthalene of formula II, according to Claim 1, is acylated in a single step forming the corresponding acyl derivative (III)



Wherein R = C₁₋₃ alkyl

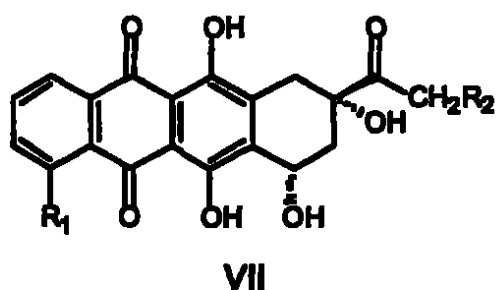
- b) the acyl derivative (III) is enantioselectively hydroxylated to form the diol (IV)



Wherein R = C₁₋₃ alkyl

Which is transformed by known methods in the tetralin of formula (I) as defined in claim 1,

- c) the above said tetralin is converted into the anthracyclinone of formula VII



wherein $R_1 = H, OH, OCH_3$, $R_2 = H, OH, O\text{-acyl}$ where the acyl is chosen among formyl, acetyl, mono-, di- or tri-chloroacetyl and this is finally converted into the anthracycline of formula VIII, as defined in Claim 1, by known techniques.

3. Process according to claim 2 wherein $R = \text{methyl}$ and $R_2 = \text{acetyl}$.

5 4. Process according to claims 2 and 3 wherein the acylation of (II) to (III) is performed in acetyl chloride in the presence of an excess of aluminium chloride at $-35^\circ\text{C} - +25^\circ\text{C}$.

5. Process according to claim 4 wherein the acylation is performed at 0°C .

6. Process according to claims 1 – 5 wherein the enantioselective dihydroxylation
10 according to step (b) is performed using catalytic quantities of osmium using the reactive AD-mix α with a further addition of an osmium salt and methanesulphonamide.

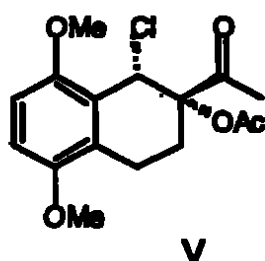
7. Process according to claim 6 wherein the osmium salt used is $K_2OsO_2(OH)_4$.

8. Process according to claim 7 wherein the reaction is performed at $-4 - +20^\circ\text{C}$.

15 9. Process according to claim 8 wherein the reaction is performed at 0°C .

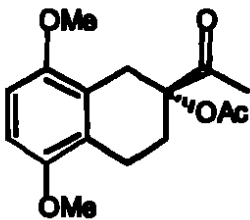
10. Process according to claims 1 – 9 wherein the anthracyclines of formula (VIII) are: daunomicin (VIII, wherein $R_1 = OCH_3$, $R_2 = H$, $R_3 = X$), doxorubicin (VIII wherein: $R_1 = OCH_3$, $R_2 = OH$, $R_3 = X$), idarubicin (VIII wherein: $R_1 = H$, $R_2 = H$, $R_3 = X$) epi-rubicin (VIII, wherein: $R_1 = OCH_3$, $R_2 = OH$, $R_3 = Y$), or a tetracycline of
20 formula VIII wherein: $R_1 = H$, $R_2 = OH$, $R_3 = Z$, where X, Y and Z are as defined in claim 1.

11. Optically active compound of formula V



25 12. Optically active compound of formula VI

15



VI

5

INTERNATIONAL SEARCH REPORT

Inter Application No
PCT/EP 01/13217

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07H15/252 C07C69/14 //C07M7:00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07H C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RAO, A. V. RAMA ET AL: "A stereoconvergent synthesis of (+)-4-demethoxydaunomycin" J. CHEM. SOC., CHEM. COMMUN. (1984), (7), 453-5 XP002188353 * the whole document, in particular page 454, compounds 2,3,6 and column 2, last paragraph * — -/-	1,9

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *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)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

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

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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.

Z document member of the same patent family

Date of the actual completion of the international search

29 January 2002

Date of mailing of the international search report

27/02/2002

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Fitz, W

INTERNATIONAL SEARCH REPORT

 Intern I Application No
 PCT/EP 01/13217

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	RHO, YOUNG S. ET AL: "Total synthesis of a new 7-deoxyidarubicinone derivative through the functionalization of an A-ring side chain" BULL. KOREAN CHEM. SOC. (2000), 21(8), 774-778 , XP001058968 * the whole document, in particular page 774, compounds 1-5, and Scheme I, compounds 6 and 14; page 775, column 2, Scheme 2; page 778, column 1, ref. 4b *	1,9
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TANNO, NORIHIKO ET AL: "Preparation of dihydroxytetrahydronaphthacenedione derivatives as intermediates for anthracycline antibiotics" retrieved from STN Database accession no. 108:21533 XP002188593 * abstract, in particular CAS RN 112007-70-2 * & JP 62 132838 A (SUMITOMO PHARMACEUTICALS CO., LTD., JAPAN) 16 June 1987 (1987-06-16)	12
Y	NAKAJIMA, M. ET AL.: "Short-step asymmetric synthesis of anthracycline antibiotics via enantioselective dihydroxylation by osmium tetroxide with a chiral diamine" TETRAHEDRON, vol. 49, no. 47, 1993, pages 10807-10816, XP002188355 cited in the application the whole document	1-3,6-12
Y	RAO, A. V. RAMA ET AL: "Total synthesis of (+)-4-demethoxydaunomycinone" INDIAN J. CHEM., SECT. B (1985), 24B(7), 697-702 , XP008000090 * the whole document, in particular page 698, Scheme 1, compounds 9 and 10; page 700, column 1, last paragraph - column 2, first paragraph *	1-3,6-12

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INTERNATIONAL SEARCH REPORT

Inte Application No
PCT/EP 01/13217

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	ARCAMONE, F. ET AL.: "Synthesis and antitumour activity of new adriamycin analogues" EXPERIENTIA, vol. 34, no. 10, 1978, pages 1255-1257, XP002188354 the whole document	1,11,12
A	US 4 077 988 A (ARCAMONE FEDERICO ET AL) 7 March 1978 (1978-03-07) * the whole document, in particular column 5, lines 25-42 *	1,11,12
A	RUSSELL, R.A. ET AL. : "An economical and versatile synthesis of 5,8-dialkoxy-2-acetyl-3,4-dihydronaphtalenes: key precursors for the synthesis of chiral anthracyclines" J. CHEM. SOC, CHEM. COMMUN., 1983, pages 994-995, XP002188356 cited in the application the whole document	1,11,12

INTERNATIONAL SEARCH REPORT

Information on patent family members

Info Application No
PCT/EP 01/13217

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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XP-002188353

A Stereoconvergent Synthesis of (+)-4-Demethoxydaunomycin†

A. V. Rama Rao,* J. S. Yadav, K. Bal Reddy, and A. R. Mahendale

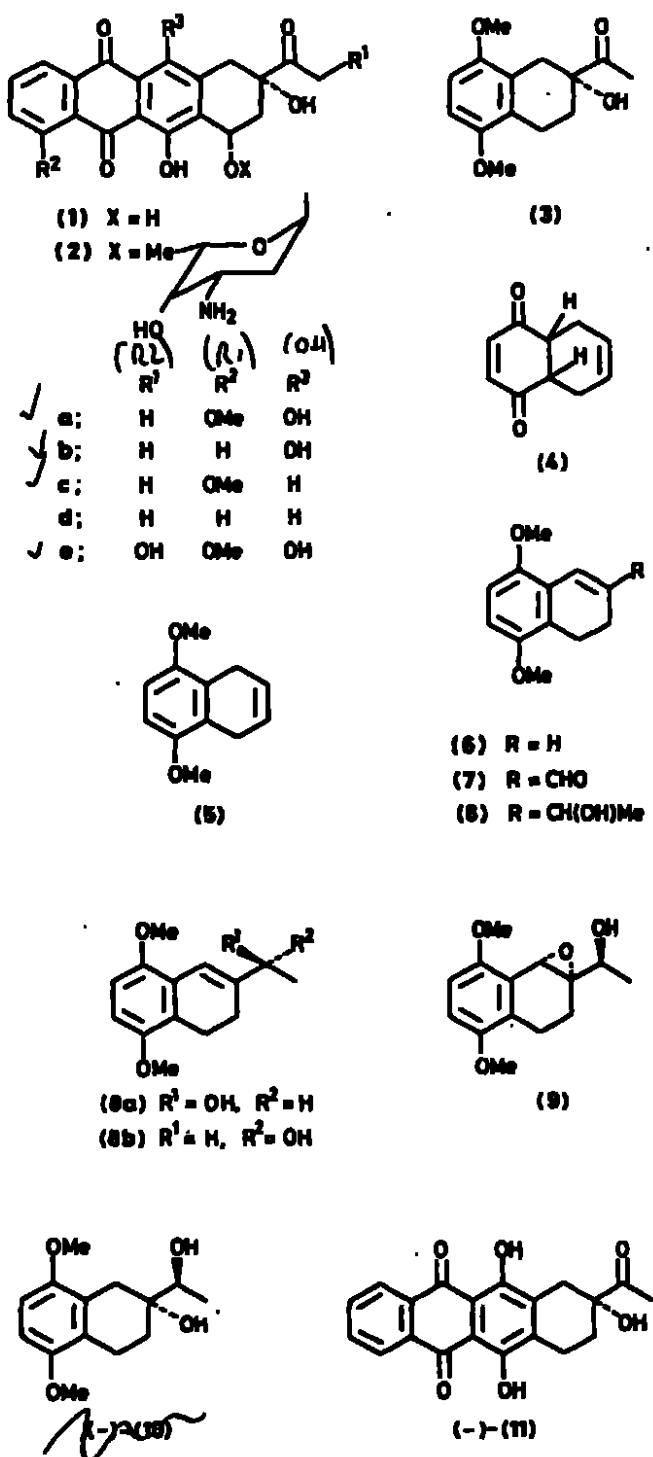
National Chemical Laboratory, Poona 411 008, India

Sharpless kinetic asymmetric epoxidation on $(\pm)$ -2-(1-hydroxyethyl)-5,8-dimethoxy-3,4-dihydronaphthalene [(8)] followed by LiAlH_4 reduction gave R -(-)-2-(S -1-hydroxyethyl)-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene [(-)-(10)] and the undesired antipode: the former was converted into R -(-)-2-acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene [R -(-)-(3)] while the latter was epimerized and recycled.

We have recently reported¹ a number of methods for the synthesis of racemic anthracyclones (1), the aglycones of antitumour anthracyclines (2), such as daunomycinone (1a),

4-demethoxydaunomycinone (1b), 11-deoxydaunomycinone (1c), and 4-demethoxy-11-deoxydaunomycinone (1d). However, studies on the structure-activity relationships have indicated that 4-demethoxydaunomycin (2b), not available by fermentation methods, is ca. 10 times more effective than natural daunomycin (2a) or adriamycin (2e) and clinical trials

† This work forms part of the Ph.D. Dissertation of K. Bal Reddy, University of Poona, July 1983.



are reported to be promising.² Although numerous syntheses of anthracyclines have been reported, the original assemblage of Wong *et al.*³ for the tetracyclic system of AB + CD coupling, making use of the key intermediate, 2-acetyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (3), has proved to be the most practical approach for the synthesis of natural and synthetic anthracyclines including (1b). Consequently, numerous approaches have been developed for the synthesis of (3) and this compound has been resolved to obtain optically pure *R*-(+)-(3).⁴ We now wish to report a practical and convenient method of preparing *R*-(+)-(3) via Sharpless asymmetric epoxidation⁵ (kinetic resolution

method) of the racemic allylic alcohol (8) prepared from benzoquinone. The undesired antipode (8b) is then epimerized and recycled. Our present method is exceptionally simple and easy to operate for the synthesis of a variety of aglycones in optically active form.

Diels-Alder reaction of benzoquinone with butadiene in acetic acid at room temperature (r.t.) afforded the adduct (4) in 90% yield.⁶ *O*-Methylation (Me₂SO₄, K₂CO₃, boiling acetone, 4 h) gave 5,8-dimethoxy-1,4-dihydronaphthalene⁷ (5). Base catalysed isomerization of (5) (Bu⁺OK, Me₂SO, r.t., N₂) resulted in the formation of 5,8-dimethoxy-3,4-dihydronaphthalene (6) in 100% yield.⁸ [Colourless crystals, hexane, m.p. 70°C, ¹H n.m.r. (CDCl₃) δ 6.83 (m, 1H, H-1), 6.63 (s, 2H, ArH), 5.85 (m, 1H, H-2), 3.80 (s, 6H, Me), 2.1–2.7 (m, 4H, H-3,4)]. Vilmeier formylation of (6) (POCl₃, *N,N*-dimethylformamide, 80°C, 4 h) gave the aldehyde (7) (m.p. 91–92°C). Grignard reaction on (7) (MeMgI, Et₂O, r.t., 1 h, N₂) afforded the (±)-2-(1-hydroxyethyl)-5,8-dimethoxy-3,4-dihydronaphthalene⁹ (m.p. 78–79°C; lit.⁸ m.p. 78–79°C).

Kinetic resolution of (±)-(8) was carried out at –55 to –50°C by treating (8) (1 mol. equiv.) in CH₂Cl₂ sequentially with titanium tetraisopropoxide (TIP), (+)-di-isopropyltartrate [L-(+)-DIPT], and *t*-butylhydroperoxide (TBHP) in a 1:1:0.6 molar ratio. The progress of the reaction was monitored by titrating the concentration of TBHP. After completion of the reaction (10 h), the reaction was quenched with aqueous acetone maintained at –50°C. Usual work up⁴ gave a mixture of two products (9) and (8b) which was directly subjected to reduction [LiAlH₄, tetrahydrofuran (THF), r.t., 4 h] followed by chromatographic separation (silica gel, benzene-acetone) to give *R*-(+)-(8b) (38% yield, m.p. 88–89°C, [α]_D²⁰ + 20.3° (c 0.5, EtOH)) and *R*-(–)-2-(*S*-1-hydroxyethyl)-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (–)-(10) (40% yield, m.p. 154–155°C, [α]_D²⁰ –49.4° (c 0.5, EtOH); lit.⁴ m.p. 154–155°C, [α]_D²⁰ –49.7° (c 0.50, EtOH)). The undesired antipode (+)-(8b) was inverted⁹ by reacting with triphenylphosphine, diethyl azodicarboxylate, and benzoic acid in THF to give the benzoate of (–)-(8a). Hydrolysis (NaOMe, MeOH, r.t., 5 h) followed by purification (silica gel, hexane-acetone) afforded (–)-(8a) (70% yield, m.p. 86–88°C, [α]_D²⁰ –18.6° (c 0.5, EtOH)). Epimerization of (–)-(8a) [CH₂Cl₂, –55 to –50°C TIP, L-(+)-DIPT, TBHP, N₂] followed by reduction with LiAlH₄ gave (–)-(10) (83% yield, m.p. 152–154°C, [α]_D²⁰ –47.6° (c 0.5, EtOH)).

Oxidation of (–)-(10) with Fetizon's reagent¹⁰ (AgCO₃, celite) gave *R*-(–)-(3) (m.p. 128–129°C, [α]_D²⁰ –48.8° (c 1, CHCl₃); lit.⁴ m.p. 130–132°C, [α]_D²⁰ –50° (c 1, CHCl₃)). Fusion of *R*-(–)-(3) with phthalic anhydride in an intimate mixture of AlCl₃-NaCl (5:1) at 180°C (2 min) and usual work up gave (–)-4-demethoxy-7-deoxydaunomycinone (11) (m.p. 227–228°C, [α]_D²⁰ –84°C (c 0.1, CHCl₃); lit.¹¹ m.p. 228–230°C, [α]_D²⁰ –87° (c 0.1, CHCl₃)).

As the conversion of (11) into (1b)¹² and subsequently into (2b) by convenient methods¹¹ has already been described, we consider that our approach constitutes a practical total synthesis of optically active (2b).

† We are thankful to our colleagues, Jaweed and Sathaye for making available large amounts of this product. After completion of this work, a similar approach has been made use of by R. A. Russell, G. W. Collins, P. S. Gee, and R. N. Warren, *J. Chem. Soc., Chem. Commun.*, 1983, 994.

All the new compounds gave satisfactory elemental and spectral analyses.

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Total Synthesis of a New 7-Deoxyidarubicinone Derivative through the Functionalization of an A-Ring Side Chain

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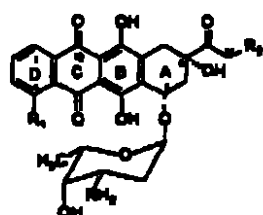
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A convenient total synthesis of a new 7-deoxyidarubicinone derivative 21, the aglycon of the anticancer antibiotic idarubicin analogue, is described. Key features of the synthesis are the Friedel-Crafts acylation and the functionalization of an A-ring side chain. A synthon 14 for the A and B rings was prepared from intermediate 6 in five steps.

Introduction

The clinical utility of the anthracycline antitumor antibiotics^{1,2,3} such as doxorubicin (adriamycin) 1, daunorubicin (daunomycin) 2, and carminomycin 3 is well established (Figure 1). However, their uses for cancer chemotherapy are seriously hampered by their side effects, especially by dose-related cardiotoxicity. Therefore, numerous synthetic efforts have been devoted to overcome these disadvantages culminating in the development of artificial 4-demethoxyadriamycin 4 and 4-demethoxydaunorubicin (idarubicin) 5, which could show improved pharmacological profile.^{1a-c} Since the biological activity of the anthracyclines is critically dependent on the functional groups at C-4, C-8, C-9, C-10, or C-14 positions in an aglycon, extensive efforts have been devoted to functionalization of these positions. Some anthracycline derivatives possessing fluorine atom or amine functions, the most interesting and promising congeners in light of the structure-activity relationship³ have been synthesized recently.^{4,7,8a,b} In more recent papers, we have also reported the successful synthesis of various anthracycline derivatives.^{5a-5c}

Herein, we describe the total synthesis of a new 7-deoxyidarubicinone derivative 21, a potential prodrug⁹ of anthracycline including an ester linkage of 14-OH in idarubicinone with a butyric acid residue. Additionally, we wish to describe the synthetic studies on an AB-synthon 14 necessary for the synthesis of the aglycon.

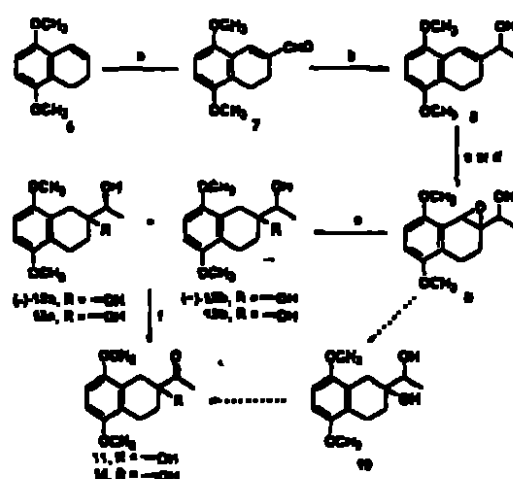


- | | |
|--------------------------|--|
| 1. Adriamycin | R ₁ = OH, R ₂ = OH |
| 2. Daunorubicin | R ₁ = OH, R ₂ = H |
| 3. Carminomycin | R ₁ = R ₂ = OH |
| 4. 4-Demethoxyadriamycin | R ₁ = H, R ₂ = OH |
| 5. Idarubicin | R ₁ = R ₂ = H |

Figure 1. Some Daunomycin Derivatives.

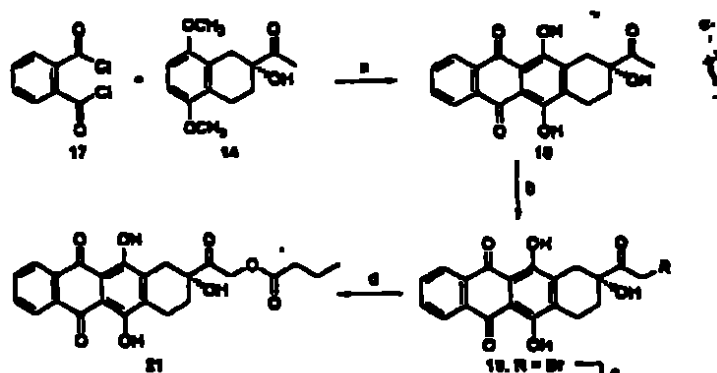
Results and Discussion

In the previous reports, we frequently used the Michael type reaction or the Friedel-Crafts acylation for the effective construction of tetracyclic skeleton in anthracycline.⁵ In this paper, we synthesized a new 7-deoxyidarubicinone derivative 21 through the Friedel-Crafts acylation^{5a,5c,16} of the preformed bicyclic AB-ring synthon 14 with D-ring phthaloyl dichloride (17) and the functionalization of C-14 site in the aglycon. For this target, our AB-synthon 14 was prepared from tetralene (6) by the sequence depicted in scheme 1. Tetralene (6) was obtained from tetralone by the known procedure.¹⁰ Dasgupta and Ghatak reported the synthesis of α,β -unsaturated aldehyde 7 from a tetralone through three steps involving β -ketoacetals.¹¹ But, we synthesized the aldehyde 7 from tetralene 6 using Vilsmeier-Haack reagent¹² in one step. The Grignard reaction of aldehyde 7 with methylmagnesium bromide gave the addition product 8. The double bond of 8 was subjected to epoxidation with various methods to produce epoxide 9. Because the epoxide 9 were apt to be converted to undesired product when the material



Scheme 1. (a) POCl₃, DMF, 0 °C. (b) CH₃MgBr, THF, 10 °C. (c) *m*-CPBA, CH₂Cl₂, -10 °C. (d) Method A) *t*-BuOOH, VO(acac)₃, PhH, rt; Method B) (+)-DIPT, Ti(OPr)₄, *t*-BuOOH, CH₂Cl₂, -78 °C → 0 °C. (e) LAH, THF, rt. (f) Ag₂CO₃ on celite, PhH, reflux.

was handled with in an air atmosphere, the mixed product was directly used in the next reduction without separation. The first attempted method was applied by *m*-chloroperbenzoic acid (*m*-CPBA) mediated epoxidation which was previously reported.^{12,14} The epoxidation of ($\pm$)-8 using *m*-CPBA for the formation of racemate 11 was not successful and the unidentified materials and reactants were mainly recovered, probably due to the instability of the structure affected by the strong oxidant to prevent the desired intermediate. The second method involved the epoxidation with *tert*-butyl hydroperoxide and a catalytic amount of vanadium oxyacetylacetonate ($\text{VO}(\text{acac})_3$) in benzene reported by Terashima *et al.*¹³ The epoxidation of the racemic allylic alcohol ($\pm$)-8 using Terashima method followed by reductive cleavage of the unstable epoxide ($\pm$)-9 was found to give the intermediate ($\pm$)-12/13 remaining some side products. The TLC spots were R_f = 0.75 (8), 0.5 (12/13), 0.3, and 0.27 (eluant: 50% ethylacetate in hexane). Therefore, we have also investigated to analyze the structure of the side products. Through a careful flash column chromatography using silica gel in hexane/ethylacetate as eluant, we could isolate diastereomeric mixture of ($\pm$)-12/13 in 45% yield based on ($\pm$)-8 and an isomer of the side compounds (15/16), which were much less than the desired products, in the ratio of about 1:5 determined by ^1H NMR analysis of the crude product. Direct recrystallization of the diastereomeric mixture of ($\pm$)-12/13 in ether afforded the major diastereomer (($\pm$)-12, 39%) in a pure state. The crude diastereomeric mixture (($\pm$)-12/13) showed the two benzylic carbons as two strong signals at 29.1 and 30.7 ppm and two peak signals at 27.3 and 33.1 ppm in the ^{13}C NMR spectrum. The integration ratio for the two sets of signals was found to be very similar to Terashima's results as 96 : 4. The last two compounds (R_f = 0.3 and 0.27) were also supposed to be diastereomers (2*R*)-15/16 having three hydroxyl groups based on the following spectroscopic and mass data: (a) two methine proton of 15 were observed at δ 5.45 (s, 1H) and 4.78–4.83 (q, 1H, J = 6.3 Hz, C-1'), whereas those of 16 were found at δ 5.08 (s, 1H) and 3.77–3.80 (q, 1H, J = 6.6, C-1'); (b) three hydroxyl protons of 15 or 16 were all disappeared when treating a few drop of D_2O ; (c) the GC/MS spectrum showed at m/z 268 (M^+), 206, 191, 164, and 149. The formation of the isomer suggest that hydrolysis of unstable epoxide 12 occur in a moisture atmosphere. The last method was attempted under Sharpless condition using (+)-diisopropyl D-tartrate ((+)-DIPT), titanium (IV) isopropoxide ($\text{Ti}(\text{OiPr})_4$), and *tert*-butyl hydroperoxide at -78°C .¹⁶ Optically pure (2*R*)-(-)-12a was obtained from 8 in 42% yield through the asymmetric epoxidation followed by reduction with lithium aluminum hydride. This method was always detected ca. 33% of unreacted material (8) due to the kinetic resolution, accompanied with small amounts of



Scheme 2. (a) AlCl_3 , PhNO_2 , $80\text{--}100^\circ\text{C}$. (b) PHT, THF, rt, 24 hr. (c) 1% NaOH, Me_2CO , reflux. (d) BuCO_2H , DCC, DMF, rt.

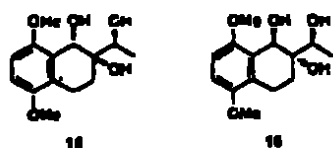
side products as described above. Oxidation of ($\pm$)-12 or (-)-12a with Fetizon reagent¹⁵ in benzene afforded ($\pm$)-11 and (-)-14 in 90% and 78% yields, respectively. The physical and spectral properties of ($\pm$)-11 or (-)-14 were identical in all respects with the literature.^{12,13a-c,14a}

DA-125 containing a β -alanine residue developed by Dong-A Pharmaceutical Co., Ltd. (KR) was prepared by nucleophilic displacement coupling using a *N*-Boc- β -alanine sodium salt and a C-14 bromodaunomycin in acetone/water. The DA-125 prodrug was found to have higher anticancer activity and less cardiotoxicity than the previously reported daunorubicin family.¹⁸ Therefore, we wish to also prepare a new anthracycline derivative through the functionalization of the C-14 position in a 7-deoxyidarubicinone. It had been previously established that phthaloyl chloride (17) could be condensed regioselectively with some AB-ring moieties in respectable yields.^{12a,16} After condensation of 17 and (-)-14 based on our published papers^{12a,c} to afford 18 in good yields, bromination of C-14 site with pyrrolidone hydrobromide (PHT) in THF¹⁷ gave 19 in 90% yield. Hydrolysis of 19 with 1% NaOH in refluxing acetone gave mainly 20 in 53% yield. The esterification¹⁹ of the product 20 with butyric acid under dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) in dry $\text{N,N'$ -dimethylformamide gave 21 (91%) as a major product and trace amount of unidentified materials. Since introduction of the 7-OH group in a 7-deoxyanthracyclines has been reported previously in two steps,^{12a-f} the developed route could provide aglycon of a new idarubicinone derivative.

Experimental Section

All reactions were run under dry nitrogen or argon atmosphere with oven-dried glassware, unless specified otherwise. All solvents were carefully dried and distilled by literature procedure²⁰ prior to use. Bulk grade hexane was distilled prior to use. Merck pre-coated silica gel plates (Art. 5554) with fluorescent indicator were used as analytical TLC. Gravity column chromatography and flash column chromatography were carried out on silica gel (230–400 mesh from Merck).

^1H NMR and ^{13}C NMR spectra were recorded on a JEOL



JNM EX-400 spectrometer. Proton chemical shifts (δ) were reported in ppm downfield from tetramethylsilane (TMS), and ^{13}C resonance were recorded using the 77.0 ppm CDCl_3 resonance of the solvent as an internal reference and reported in ppm downfield from TMS. Infrared spectra were recorded on a Nicolet S-DXB series FT-IR spectrophotometer. Mass spectra were obtained on a JEOL JMX-DX 300 spectrometer by the electron impact or a Hewlett Packard 5972 series mass selective detector. Optical rotations were measured with JASCO DIP-360 spectrophotometer. Melting points were determined in capillary tubes on a Büchi 510 melting point apparatus and were uncorrected.

5,8-Dimethoxy-3,4-dihydro-2-naphthalencarbaldehyde (7). Phosphorus oxychloride (6.30 mL, 67.6 mmol) was added slowly to stirred dimethylformamide (20 mL) at 0°C . The mixture was warmed to room temperature, stirred for 20 min, cooled to 0°C , and added dropwise via a double-tipped needle into a solution of naphthalene 6^{10} (8.57 g, 45.0 mmol) in dimethylformamide (50 mL) at 0°C . The ice bath was removed, and the orange reaction mixture was heated to reflux for 2-3 hrs. After cooling to 0°C , a solution of sodium acetate (24.52 g, 0.18 mol) in water (80 mL) was added slowly. The mixture was refluxed for 30 min, cooled to room temperature, and extracted with diethyl ether (2×100 mL). The combined organic layers were washed with water, saturated aqueous sodium bicarbonate, and brine. After drying over anhydrous magnesium sulfate, the solution was concentrated to give **7** (7.17 g, 73%) as light yellow needles: mp $92-94^\circ\text{C}$; $^1\text{H-NMR}$ (CDCl_3) δ 9.76 (s, 1H, CHO), 7.70 (s, 1H), 6.88 (d, $J = 8.79$ Hz, 1H, ArH), 6.76 (d, 1H, $J = 8.79$ Hz, ArH), 3.85 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 2.84 (t, 2H, $J = 6.54$ Hz, CH_2), 2.50 (t, 2H, $J = 6.54$ Hz, CH_2); $^{13}\text{C-NMR}$ (CDCl_3) δ 193.01, 150.92, 150.26, 140.36, 138.02, 127.43, 122.09, 113.86, 108.50, 56.05, 55.84, 20.01, 18.19; IR (film) 3052, 3005, 2952, 2824, 1655, 1481, 1252, 1085 cm^{-1} ; MS (m/z) 218 (M^+), 189 ($M-29$), 174, 159, 144, 131, 115.

($\pm$)-1-(5,8-Dimethoxy-3,4-dihydro-2-naphthalenyl)-1-ethanol (8). To a stirred solution of aldehyde **7** (8.97 g, 41.1 mmol) in tetrahydrofuran (100 mL) at 10°C was added dropwise a solution of methylmagnesium bromide (20.5 mL, 61.6 mmol, 3.0 M in ether) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 1 hr. After completion of the reaction by monitored on TLC, saturated aqueous ammonium chloride was added and the mixture was extracted with ether (2×100 mL). The extracts were combined, dried over anhydrous magnesium sulfate, and evaporated. The residue was recrystallized from cyclohexane to give **8** as colorless needles (8.67 g, 90%): mp 78°C ; $^1\text{H-NMR}$ (CDCl_3) δ 1.34 (d, 3H, $J = 6.35$ Hz, CH_3), 2.25 (m, 2H, CH_2), 2.44 (s, 1H, OH), 2.76 (m, 2H, CH_2), 3.77 (s, 6H, 2OCH_3), 4.42 (q, 1H, $J = 3.4$ Hz, CH), 6.68 (d, 1H, ArH), 6.64 (d, 1H, ArH), 6.77 (s, 1H, CH); $^{13}\text{C-NMR}$ (CDCl_3) δ 150.3, 149.4, 143.8, 124.5, 123.9, 115.3, 109.7, 108.5, 77.4, 56.0, 22.17, 21.5, 20.9; IR (film) 3402, 2938, 2838, 1474, 1252, 1098 cm^{-1} ; MS (m/z) 234, 216 ($M-18$), 201, 175, 141, 128, 115.

1-(4,7-Dimethoxy-1a,2,3,7b-tetrahydronaphtho[1,2-b]

oxiren-1-yl)-1-ethanol (9).

Attempted condition with ($\pm$)-**8** and *m*-CPBA: A mixture of **8** (300 mg, 1.28 mmol) and *m*-CPBA (70%, 0.344 g, 1.54 mmol) was dissolved in 50 mL of methylene chloride and stirred at -10°C for 2 hrs. The reaction mixture was diluted with 50 mL of methylene chloride and washed successively with 10% aqueous sodium carbonate solution and brine, dried over anhydrous sodium sulfate. This method was attempted under several different conditions. But, neither of these procedures was successful for the epoxidation, and only unidentified materials were mainly obtained.

(1S)-1-[(1aR,7bR)-4,7-Dimethoxy-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxiren-1-yl]-1-ethanol (($\pm$)-9). *tert*-Butyl hydroperoxide (0.46 mL, 6.0 M solution in decane, 2.77 mmol) was added to a mixture of ($\pm$)-**8** (0.72 g, 3.07 mmol) and vanadium oxyacetylacetonate (0.11 g, 0.43 mmol) in benzene (100 mL), and the whole was stirred at room temperature for 45 min. Concentration *in vacuo* gave a crude mixture as a yellow oil. Because the resulting mixture was quite unstable, the mixed product was immediately used for the next reduction without further purification.

(1S)-1-[(1aR,7bR)-4,7-Dimethoxy-1a,2,3,7b-tetrahydronaphtho[1,2-b]oxiren-1-yl]ethanol ((-)-9). (+)-Diisopropyl D-tartrate (89.8 μL , 0.43 mmol) was added at -75°C to a solution of titanium (IV) isopropoxide (127.0 μL , 0.43 mmol) in methylene chloride (20 mL) under argon atmosphere. A solution of the olefin **8** (0.5 g, 2.13 mmol) in 10 mL of methylene chloride was then added, and the resulting mixture was stirred at -75°C for 30 min. *tert*-Butyl hydroperoxide (356.0 μL of 6.0 M solution in decane, 2.13 mmol) was then added over a period of 15 min, and the reaction mixture was stirred at -75°C for 1 hr, and allowed to reach 0°C over a further period for 2 hrs. The organic solvent was concentrated by a rotavapor to give (-)-**9** as oil that could be used directly in the preparation of (-)-**12a** without further separation.

2-(1-Hydroxyethyl)-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenol (($\pm$)-12) and Its Isomer (($\pm$)-13) from ($\pm$)-9. A solution of above crude ($\pm$)-**9** (0.75 g, 3.01 mmol) in tetrahydrofuran (5 mL) was added dropwise to a suspension of lithium aluminum hydride (0.23 g, 6.06 mmol) in tetrahydrofuran (10 mL) at 0°C and the whole was stirred at room temperature for 8 hrs. The reaction mixture was allowed to warm to room temperature before being cooled to 0°C , quenched with 2N-sodium hydroxide (50 mL), and the upper organic phase was separated. The aqueous phase was further extracted with ethylacetate. The organic extracts were combined and washed successively with water and brine, and dried over magnesium sulfate. Filtration and concentration *in vacuo* gave a crude mixture of two pair of diastereomers (12/13, 15/16), which was purified by flash chromatography (hexane/ethylacetate = 2/1 $\rightarrow$ 1/1) to give **15** (ca. 3.6%), **16** (ca. 18.1%), and 12/13 (0.35 g, 45.2% from **8**) as a white powder. Since separation of the a diastereomeric mixture of ($\pm$)-12/13 (mp $142-148^\circ\text{C}$) was not carried out throughout purification, this sample should consist of the two diastereomers in the ratio of 96 : 4 determined by ^{13}C NMR analysis of two benzylic carbons. The ^{13}C NMR spec-

trum of this sample supported this assumption. ^{13}C NMR (in CDCl_3): 29.1 (C_1 or C_4), 30.7 (C_1 or C_4) for ($\pm$)-12 and 27.3 (C_1 or C_4), 33.1 (C_4 or C_1) for ($\pm$)-13 (this ratio of two sets of signals was 96 : 4). The remaining portion of the crystals (350 mg) was directly recrystallized from diethyl ether to give pure ($\pm$)-12a as white crystals (302 mg, 39%): mp 150–153 °C, (lit.^{13b} 154–155 °C); ^1H -NMR (CDCl_3) δ 1.28 (d, 3H, $J = 6.3$ Hz, CH_3), 1.57–1.98 (m, 2H, CH_2), 2.59–2.54 (two s, 2H, OH), 2.70–3.00 (m, 4H), 3.72 (q, 1H, $J = 6.3$ Hz, methine H), 3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 6.64 (s, 2H, ArH); ^{13}C -NMR (CDCl_3) δ 151.9, 151.3, 126.1, 124.2, 107.1, 72.8, 72.2, 55.6, 30.7, 29.1, 19.8, 17.1; IR (film) 3338, 2945, 1481, 1252, 1084 cm^{-1} ; GC/MS (m/z) 252 (M^+), 234 ($M^+ - \text{H}_2\text{O}$), 207 (100), 189 (38), 175.

(1 S^* ,2 R^*)-2-[(1 S^*)-1-Hydroxyethyl]-5,8-dimethoxy-1,2,3,4-tetrahydro-1,2-naphthalenediol (($\pm$)-15). Spectral data of ($\pm$)-15: ^1H -NMR (CDCl_3) δ 1.31 (d, 3H, $J = 6.35$ Hz, CH_3), 1.68–1.74 (m, 1H, CH), 1.80 (bs, 1H, OH), 2.08–2.15 (m, 1H, CH), 2.20 (bs, 1H, OH), 2.61–2.69 (m, 1H, CH), 2.96–3.01 (m, 1H, CH), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 4.78–4.83 (q, 1H, $J = 6.35$ Hz, methine H), 5.45 (s, 1H, methine H), 6.67 (d, 1H, $J = 8.79$ Hz, ArH), 6.78 (d, 1H, $J = 8.79$ Hz, ArH); GC/MS (m/z) 268 (M^+), 206 (100), 191, 180, 164, 149.

(1 R^* ,2 S^*)-2-[(1 S^*)-1-Hydroxyethyl]-5,8-dimethoxy-1,2,3,4-tetrahydro-1,2-naphthalenediol (($\pm$)-16). Spectral data of ($\pm$)-16: ^1H -NMR (CDCl_3) δ 1.30 (d, 3H, $J = 6.35$ Hz, CH_3), 1.64–1.71 (m, 1H, CH), 1.93–2.05 (m, 1H, CH), 2.55 (bs, 1H, OH), 2.71–2.89 (m, 2H, CH_2), 3.29 (bs, 1H, OH), 3.77–3.80 (q, 1H, $J = 6.83$ Hz methine H), 3.78 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.25 (bs, 1H, OH), 5.08 (s, 1H, methine H), 6.71 (s, 2H, ArH); GC/MS (m/z) 268 (M^+), 206 (100), 191, 180, 164, 149.

(2 R)-2-[(1 S)-1-Hydroxyethyl]-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenol (($\pm$)-12a). Reaction of above unstable ($\pm$)-9 and lithium aluminum hydride (20.0 mg, 0.53 mmol) in tetrahydrofuran (20 mL) as described for the preparation of ($\pm$)-9 yielded unreacted 8 (0.17 g, ca. 33% recovered), ($\pm$)-13 (0.23 g, 42% yield from 8) as a pale yellow oil that crystallized on standing, mp 128–130 °C (white powder from ether/hexane), and small amounts of 15 and 16. The compound ($\pm$)-12a had ^1H and ^{13}C NMR, IR, and mass data as reported above, $[\alpha]_D^{20} -36.7^\circ$ ($c = 0.9$, CH_3OH). (lit.^{13b} $[\alpha]_D -49.7^\circ$ ($c = 0.5$, ethanol), lit.^{14a} $[\alpha]_D -34.3^\circ$ ($c = 1.2$)).

1-[2-Hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenyl]-1-ethanone (($\pm$)-11). Fetizon reagent (silver carbonate on celite 50 wt %), 1.0 mmol of Ag_2CO_3 on 1.0 g of the reagent¹⁵ (8.52 g, 8.52 mmol) was added to a benzene solution (50 mL) of ($\pm$)-12 (0.43 g, 1.70 mmol), and the mixture was heated at reflux for 30 min, then cooled. An insoluble material was filtered off and washed with benzene (50 mL). The combined filtrate and washings were concentrated *in vacuo*, giving brown oil. The residue was purified by flash chromatography (hexane/ethylacetate = 3/1) to give 11 (0.38 g, 90%) as colorless crystals: mp 100–102 °C; ^1H -NMR (CDCl_3) δ 1.83–2.05 (m, 2H, CH), 2.32 (s, 3H, CH_3), 2.75–2.99 (m, 4H), 3.62 (s, 1H, OH), 3.76 (s, 3H, OCH_3),

3.79 (s, 3H, OCH_3), 6.64 (d, 1H, $J = 8.79$ Hz, ArH), 6.67 (d, 1H, $J = 8.79$ Hz, ArH); IR (film) 3480, 1700, 1492 cm^{-1} ; GC/MS (m/z) 250 (M^+), 232 ($M^+ - \text{H}_2\text{O}$), 207 (100). Those spectral properties were identical with those reported.^{13a,13b}

1-[(2 R)-2-Hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthalenyl]-1-ethanone (($\pm$)-14). Oxidation of ($\pm$)-12a (230 mg, 0.91 mmol) with Fetizon reagent¹⁵ (3.64 g, 3.64 mmol) as described for the preparation of ($\pm$)-11 yielded 177 mg (78%) of optically pure ($\pm$)-14 after purification by crystallization in hexane: mp 128–130 °C; $[\alpha]_D^{20} -48.2^\circ$ ($c = 0.98$, CHCl_3), (lit.^{13b} mp 127–128.5 °C, $[\alpha]_D^{20} -49.7^\circ$ ($c = 0.5$, ethanol), lit.^{14a} 128–129 °C $[\alpha]_D^{20} -48.8^\circ$ ($c = 1.0$, CHCl_3)). This sample exhibited the same spectral (IR, ^1H NMR, and mass data) properties^{13b,c,14a} as described above.

(8 R)-8-(2-Bromoacetyl)-6,8,11-trihydroxy-5,7,8,9,10,12-hexahydro-5,12-naphthacenedione (19). 7-Deoxydarubicinone ($\pm$)-18 ($[\alpha]_D^{20} -84.4^\circ$ ($c = 0.1$, CHCl_3), 97%ee, lit.^{13b} $[\alpha]_D^{20} -87.0^\circ$ ($c = 0.12$, CHCl_3) (0.35 g, 0.99 mmol) which was successfully obtained from previously reported papers^{13a,14c} and pyrrolidone hydrotribromide (0.54 g, 1.09 mmol) were placed in tetrahydrofuran (50 mL) and stirred at 23 °C for 24 hrs. The reaction mixture was diluted with methylene chloride (50 mL), washed with water and brine, dried over anhydrous magnesium sulfate. The mixture was concentrated *in vacuo* to give red residue 19 (0.37 g, 86%); mp 170–171 °C; ^1H -NMR (CDCl_3) δ 13.44 (s, 2H, OH), 8.34 (m, 2H, ArH), 7.84 (m, 2H, ArH), 4.38 (s, 2H, CH_2), 2.86–3.25 (m, 4H, CH_2), 2.05–2.19 (m, 2H, CH_2); GC/MS (m/z) 431 (M^+), 413, 352.

(8 R)-8-Glycolyl-6,8,11-trihydroxy-5,7,8,9,10,12-hexahydro-5,12-naphthacenedione (20). A red residue 19 (0.30 g, 0.70 mmol) was dissolved in acetone (30 mL). After the acetone solution had been made alkaline (pH = 8) by the addition of 1% NaOH (1 mL), it was refluxed for 10 min and concentrated *in vacuo*. Water was added to the residue, and the aqueous mixture was extracted with methylene chloride, washed with water and brine, dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford crude product as a solid. Flash column chromatography (hexane/ethylacetate = 1/1) afforded a pure 20 (0.21 g, 80%) as red powder: mp 192 °C; $[\alpha]_D^{20} +49.9^\circ$ ($c = 0.004$, CH_3OH); ^1H -NMR ($\text{DMSO}-d_6$) δ 13.44 (s, 2H, OH), 8.34 (m, 2H, ArH), 7.72 (m, 2H, ArH), 4.75 (s, 2H, CH_2), 2.86–3.25 (m, 4H, $2 \times \text{CH}_2$), 2.05–2.19 (m, 2H, CH_2); IR (film) 3449, 2918, 2851, 1736, 1676, 1588, 1461, 1259, 1165, 1071 cm^{-1} ; GC/MS (m/z) 368 (M^+), 350 ($M^+ - \text{H}_2\text{O}$), 310, 292.

2-Oxo-2-[(2 R)-2,5,12-trihydroxy-6,11-dioxo-1,2,3,4,6,11-hexahydro-2-naphthacenyl]ethyl butyrate (21). Dicyclohexylcarbodiimide (0.42 g, 2.04 mmol) was added to a solution of 7-deoxydarubicinone 20 (0.25 g, 0.68 mmol), butyric acid (124.0 μL , 1.36 mmol), and catalytic amount of 4-dimethylaminopyridine (DMAP) (0.10 g, 0.81 mmol) in dry dimethylformamide (15 mL). The reaction mixture was allowed to stir at room temperature for 6 hrs, at which time the mixture was evaporated *in vacuo*. The residue was dissolved in methylene chloride (50 mL) and washed with water (80 mL) and brine (2×50 mL). After drying over magne-

sium sulfate, flash column chromatography (hexane/ethyl-acetate = 3/1) gave 21 (0.27 g, 90.6%) as a red solid: mp 169-170 °C; $^1\text{H-NMR}$ (CDCl_3) δ 13.48 (s, 2H, ArOH), 8.33-8.34 (m, 2H, ArH), 7.81-7.84 (m, 2H, ArH), 5.1 (s, 2H, CH_2), 2.9-3.6 (m, 4H, $2 \times \text{CH}_2$), 2.45 (t, 2H, $J = 7.32$ Hz, CH_2), 1.93-2.34 (m, 2H, CH_2), 1.63-1.83 (m, 2H, $J = 7.32$ Hz, 7.81 Hz, CH_2), 1.01 (t, 3H, $J = 7.32$ Hz, 7.81 Hz, CH_3); IR (film) 3429, 2925, 2858, 1723, 1635, 1582, 1467, 1273, 1085, 1017 cm^{-1} ; GC/MS (m/z) 438 (M^+), 420 ($M^+ - \text{H}_2\text{O}$), 368.

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 DN - 108:21533
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 SO - Jpn. Kokai Tokkyo Koho, 9 pp.
 CODEN: JKXXAF
 DT - Patent
 LA - Japanese
 IC - ICM C07C050/38
 ICS C07C046/02;C07C69/757;C07C102/00;C07C103/42;C07C103/78
 ICA - C07H015-252
 CC - 25-28 (Benzene, Its Derivatives, and Condensed Benzenoid Compounds)
 Section cross-reference(s): 1, 26
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	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PN -	JP62132838	A	19870616	JP 1985-272230	19851203
GI -	JP63046061B	B	19880913		

[--00000031]

AB The title compds. [I; R1 = Ac, alkoxycarbonyl; R2 = OR3, NHCOR4 wherein R3 = H, hydroxy-protecting group; R4 = alkyl, haloalkyl, (halo)Ph], useful intermediates for anthracycline antibiotics, were prepd. by Friedel-Crafts reaction of Tetraline derivs. II with o-C6H4(COCl)2 in the presence of a Lewis acid. A mixt. of Tetraline deriv. 1-II (R1 = .beta.-Ac, R2 = .alpha.-NHAc) 100, o-C6H4(COCl)2 83.6, and AlCl3 229 mg in 5 mL (CH2Cl)2 was stirred for 3 h at room temp. to give 90.4% naphthacenedione deriv. 1-I (R1 = .beta.-Ac, R2 = .alpha.-NHAc).

ST naphthacenedione dihydroxy prepn anthracycline intermediate; anthracycline antibiotic intermediate dihydroxytetrahydronaphthacene prepn; phthaloyl chl ride Friedel Crafts naphthalene

IT Friedel-Crafts reaction
 (of tetrahydronaphthalene derivs., with phthaloyl chloride)

IT Antibiotics
 (anthracycline, intermediates for, dihydroxytetrahydronaphthacenedione derivs. as)

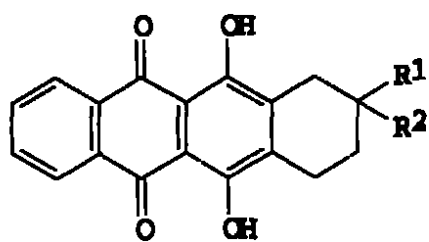
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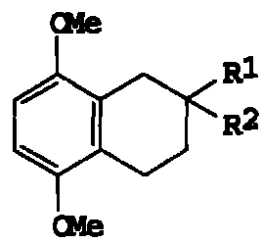
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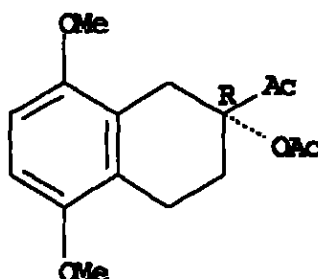


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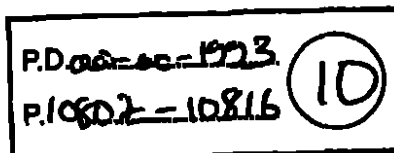
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Short-Step Asymmetric Syntheses of Anthracycline Antibiotics via Enantioselective Dihydroxylation by Osmium Tetroxide with a Chiral Diamine

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Abstract: Short-step asymmetric syntheses of (+)-7-dehydroxy-4-demethoxydaunomycinone 4 and (-)-9-deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyl-daunomycinone 5 were accomplished via enantioselective dihydroxylation by osmium tetroxide with chiral diamine 13.

The clinical utility of the anthracycline antitumor antibiotics such as adriamycin (doxorubicin) 1 and daunomycin (daunorubicin) 2 is well established.¹ The 4-demethoxy series of compounds 4 and 5 have been developed as artificial anthracyclines of improved pharmacological profile. Since the biological activity of the anthracyclines is critically dependent on the chirality at C-9, extensive efforts have been devoted to asymmetric construction of this chiral center in the desired absolute configuration.^{2, 3}

We have reported the highly enantioselective dihydroxylation of olefins by osmium tetroxide with a chiral diamine 13.⁴ Employing our system, diols of exceptionally high ee can be obtained from mono-, trans-di-, and trisubstituted olefins. The enantioface selection is shown by the general presentation in Fig. 2. Since both (+)- and (-)-13 are readily accessible in optically pure form, this method provides a powerful tool for the synthesis of optically active alcohols in high-ee with desired absolute configuration from achiral olefins. In order to demonstrate the synthetic utility of our method, asymmetric syntheses of the anthracyclines were examined. We describe herein the details of successful short-step asymmetric syntheses of (+)-7-dehydroxy-4-demethoxydaunomycinone 4 and its hydroxymethyl analog (-)-9-deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyl-daunomycinone 5.

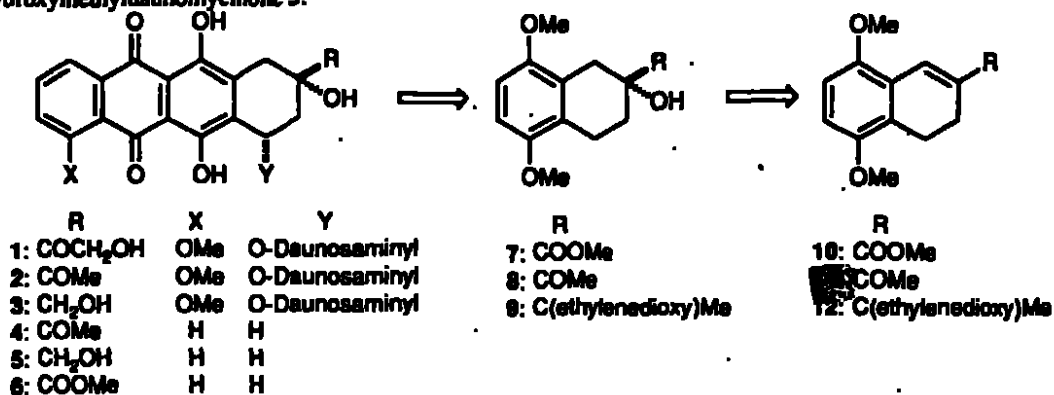


Fig. 1. Asymmetric Syntheses of Anthracyclines.

Synthetic Plan

Optically active 7 and 8 are the most common key intermediates for the synthesis of anthracyclines because it can be easily transformed into tetracycline skeleton by Friedel-Crafts condensation to afford 6 and 4, respectively. Our original plan for the asymmetric synthesis of 7 and 8 is to construct the stereocenter by enantioselective dihydroxylation of 10 and 11 followed by reductive removal of benzylic hydroxyl group. Applying the general presentation of the asymmetric dihydroxylation in Fig. 2, (-)-13 should be employed as a chiral diamine in order to obtain 7 and 8 with desired absolute configuration.

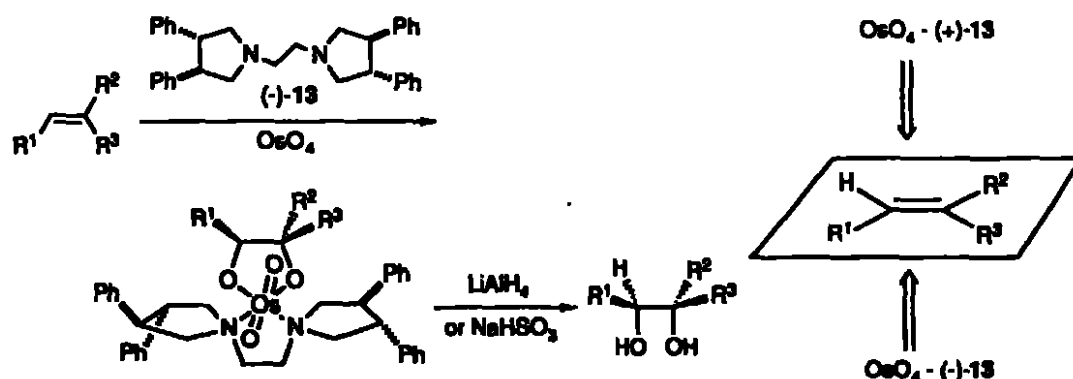


Fig. 2. Enantioselective Dihydroxylation of Olefins with OsO_4 with Chiral Diamine 13

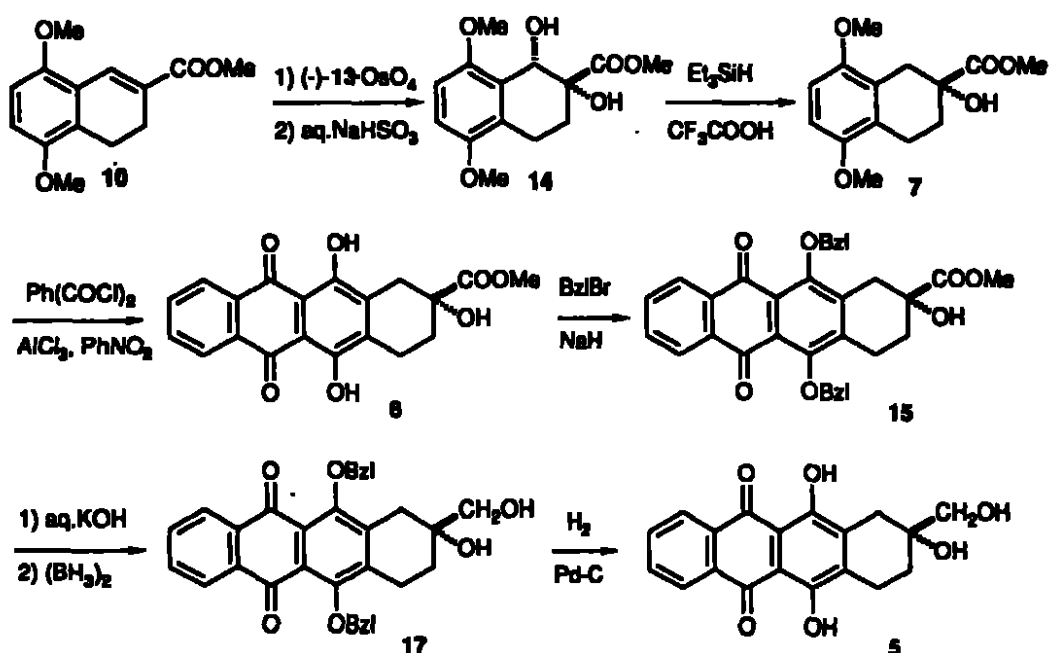
Enantioselective dihydroxylation of dihydronaphthalenes was studied with regard to the effect of vinylic substituents on efficiency in asymmetric induction. Treatment of dihydronaphthalene with osmium tetroxide (1.1 eq) in the presence of (-)-13 (1.2 eq) in THF (0.01 M) at -110°C for 6 h and the following reductive hydrolysis of the resultant osmate with sodium bisulfite in refluxing aqueous THF, provided the corresponding diol. The optical purity and absolute configuration were determined by their conversion to 7 and 8. As shown in Table 1, both 10 and 11 were oxidized in satisfactory ee with predicted absolute configuration (Run 1, 2). However, dihydroxynaphthalene with an ethylene acetal group provided the diol in only 36 % ee (Run 3). The steric size of the substituents apparently affected the enantioselectivity. Since 7 and 8 are the important key intermediates for the synthesis of anthracyclines, this enantioselective dihydroxylation was proved to be effective in constructing the requisite chiral centers of anthracyclines. The successful results in the enantioselective dihydroxylation of 10 and 11 prompted us to accomplish the asymmetric syntheses of (-)-9-deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyl-daunomycinone 5 from 10 and (+)-7-dehydroxy-4-demethoxy-daunomycinone 4 from 11.

Table 1. Enantioselective Dihydroxylation of Dihydronaphthalenes by OsO_4 with (-)-13

Run	Olefin	$[\alpha]_D^{25}(\text{CHCl}_3) (^\circ)$	ee (%)	yield (%)
1	10	-35.3	85	96
2	11	-17.6	82	96
3	12	-24.5	36	77

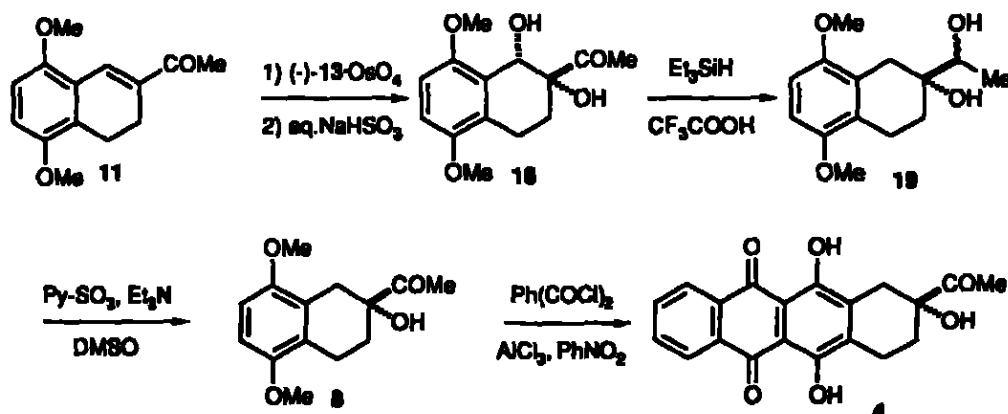
Synthesis of 9-Deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyl-daunomycinone 5

Total synthesis of (-)-9-deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyl-daunomycinone **5** was performed as shown in Scheme 1. The diol **14** obtained by enantioselective dihydroxylation was treated with triethylsilane in trifluoroacetic acid to provide **7** (85 % ee, $[\alpha]_D^{20}$ -29.5° (CHCl₃); lit.⁵ $[\alpha]_D^{20}$ -34.5° (CHCl₃)) in 94 % yield. Friedel-Crafts condensation was carried out with phthaloyl dichloride-aluminum chloride in nitrobenzene⁶ to provide tetracyclic core skeleton **6**. Recrystallization from toluene gave practically optically pure **6** ($[\alpha]_D^{20}$ -57.2° (CHCl₃); lit.⁷ $[\alpha]_D^{25}$ -60.0° (CHCl₃)) in 68 %. This three-step procedure is the shortest route via asymmetric synthesis to obtain **6**, which is a versatile key intermediate for the synthesis of anthracyclines with correct absolute configuration. We transformed **6** into 9-deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyl-daunomycinone **5**. To overcome the solubility problem, **6** was benzylated with benzyl bromide to obtain **15**. Reduction of ester was performed by successive hydrolysis and diborane reduction. Debenzilation by catalytic hydrogenation afforded optically pure **5** ($[\alpha]_D^{25}$ -31° (dioxane), lit.^{3k} ($[\alpha]_D^{25}$ -32° (dioxane)) in overall 22 % yield from **6**.

Scheme 1. Asymmetric Synthesis of **5***Synthesis of 7-Dehydroxy-4-demethoxydaunomycinone 4*

Total synthesis of (+)-7-dehydroxy-4-demethoxydaunomycinone **4** was performed as shown in Scheme 2. The diol **18** obtained by enantioselective dihydroxylation was treated with triethylsilane in trifluoroacetic acid to provide **19** as a 3:4 diastereomeric mixture which was then oxidized with sulfur trioxide-pyridine complex and triethylamine in dimethylsulfoxide to afford **8** (82 % ee, $[\alpha]_D^{25}$ -39.3° (CHCl₃); lit.⁵ $[\alpha]_D^{25}$ -48.2° (CHCl₃)) in 68 % overall yield. Friedel-Crafts condensation with phthaloyl dichloride-aluminum chloride in nitrobenzene⁶ to provide the tetracyclic core skeleton **4**. Recrystallization from benzene afforded **4** ($[\alpha]_D^{20}$ +150° (dioxane); lit.⁹

$[\alpha]_D^{20} +157^\circ$ (dioxane)) in optically pure form. The present four-step asymmetric synthesis in optically pure form constitutes the shortest route to 4. Elaboration of 4 to 4-demethoxydaunomycin is established technology.⁹



Scheme 2. Asymmetric Synthesis of 4

Summary

The shortest asymmetric syntheses of (+)-7-dehydroxy-4-demethoxydaunomycinone 4 and (-)-9-deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyl-daunomycinone 5 were accomplished via enantioselective dihydroxylation by osmium tetroxide with chiral diamine 13. These syntheses proved that enantioselective dihydroxylation mediated by the chiral diamine 13 is effective in constructing the requisite chiral centers of the target molecules.

Experimental Section

Melting points were measured using a Büchi 510 melting point apparatus and are not corrected. Optical rotations were taken with a JASCO DIP-370 digital polarimeter. IR spectra were taken with a JASCO IRA-1 infrared spectrometer and expressed in cm^{-1} . $^1\text{H-NMR}$ spectra were taken with a JEOL FX-100 spectrometer at 100MHz. Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet, br, broad. MS spectra were taken with a JEOL DX-300 mass spectrometer.

(1*S*,2*R*)-Methyl 1,2,3,4-Tetrahydro-1,2-dihydroxy-5,8-dimethoxynaphthalene-2-carboxylate (14)

To a cooled (-78°C) solution of the chiral diamine (-)-13 (80 mg, 0.17 mmol) in THF (6 ml) was added a solution of osmium tetroxide (40 mg, 0.16 mmol) in THF (3 ml). A solution of 10 (37 mg, 0.14 mmol) in THF (5 ml) was added to the bright wine-red solution above at -110°C and the whole was stirred for 6 h at the same temperature. Sodium bisulfite (1.0 g) and water (2 ml) was added to the reaction mixture and the whole was stirred for 10 h under reflux. The reaction mixture was basified with NaHCO_3 and concentrated. The residue

was suspended in ethyl acetate (50 ml) and filtered through Celite pad. The water layer of the filtrate was extracted with ethyl acetate (20 ml x2) and combined organic layer was washed with brine and dried over Na_2SO_4 . Concentration and following purification by silica gel column chromatography (benzene-ethyl acetate, 10/1 to 1/1) gave chiral diamine 13 (77 mg, 96 %) and diol 14 (40 mg, 95 %) as a caramel of $[\alpha]_{\text{D}}^{25} -35.3^\circ$ ($c=0.80$, CHCl_3). IR (CHCl_3): 3550, 1740. $^1\text{H-NMR}$ (CDCl_3) δ : 2.0-2.3 (2H, m, CH_2), 2.8-3.0 (2H, m, CH_2), 3.7-3.9 (1H, m, OCH_3 , OH), 5.29 (1H, s, CH), 6.73 (2H, s, Ar). MS m/z : 282 (M^+). HRMS Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_6$: 282.1100. Found: 282.1068.

(2R)-Methyl 1,2,3,4-Tetrahydro-2-hydroxy-5,8-dimethoxy-naphthalene-2-carboxylate (7)

A mixture of diol 14 (23 mg, 0.078 mmol), triethylsilane (0.016 ml, 0.093 mmol), and trifluoroacetic acid (0.4 ml) was stirred at 0°C for 20 min. Saturated NaHCO_3 (10 ml) and ethyl acetate (30 ml) was added to the mixture and the organic layer was washed with saturated NaHCO_3 and brine. After drying over Na_2SO_4 and concentration, the residue was purified by silica gel column chromatography (hexane-ethyl acetate, 20/1) to afford 7 (20.3 mg, 94 %) as a caramel of $[\alpha]_{\text{D}}^{20} -29.5^\circ$ ($c=2.03$, CHCl_3), [85 %ee, lit.⁵ $[\alpha]_{\text{D}}^{20} -34.5^\circ$ ($c=1.24$, CHCl_3)]. IR (CHCl_3): 3550, 1730. $^1\text{H-NMR}$ (CDCl_3) δ : 1.9-2.1 (2H, m, CH_2), 2.7-3.0 (5H, m, CH_2 , OH), 3.76 (3H, s, CH_3O), 3.78 (3H, s, CH_3O), 3.82 (3H, s, CH_3O), 6.64 (2H, s, Ar). MS m/z : 267 (MH^+), 266 (M^+), 248 ($\text{M}^+ - \text{H}_2\text{O}$).

(2R)-Methyl 1,2,3,4,6,11-Hexahydro-2,5,12-trihydroxy-6,11-dioxonaphthacene-2-carboxylate (6)

To a solution of 7 ($[\alpha]_{\text{D}}^{20} -29.5^\circ$ ($c=2.03$, CHCl_3), 85 %ee, 10 mg, 0.038 mmol) in nitrobenzene (1 ml) was added a solution of aluminum chloride (10 mg, 0.075 mmol) in nitrobenzene (1 ml) and the mixture was stirred for 30 min at room temperature. Phthaloyl dichloride (7.6 mg, 0.037 mmol) was added to the resulting green solution and the whole was stirred at 100°C for 30 min. 0.2N oxalic acid (10 ml) and ethyl acetate (20 ml) were added to the resulting purple solution and the whole was filtered through Celite pad. The water layer was extracted with ethyl acetate (20 ml x3) and the combined organic layer was washed with saturated NaHCO_3 (20 ml x2), brine (20 ml). After drying over MgSO_4 , concentration followed by silica gel column chromatography (benzene-dichloromethane, 1/4) afforded 6 (11.0 mg, 80 %) as red prisms of mp $198-205^\circ\text{C}$. $[\alpha]_{\text{D}}^{20} -51.0^\circ$ ($c=0.10$, CHCl_3), (85 %ee). Recrystallization from toluene (0.1 ml) at -78°C gave red prisms (9.4 mg, 68 %) of mp $209-210^\circ\text{C}$. $[\alpha]_{\text{D}}^{20} -57.2^\circ$ ($c=0.10$, CHCl_3). [lit.⁷ mp $210.5-211.5^\circ\text{C}$, $[\alpha]_{\text{D}}^{25} -60.0^\circ$ ($c=0.10$, CHCl_3)]. IR (KBr): 1730, 1620, 1590. $^1\text{H-NMR}$ (CDCl_3) δ : 2.0-2.2 (2H, m, CH_2), 2.9-3.1 (5H, m, CH_2 , OH), 3.88 (3H, s, CH_3O), 7.8-7.9 (2H, m, Ar), 8.3-8.4 (2H, m, Ar), 13.49 (2H, s, ArOH). MS m/z : 368 (M^+).

(2R)-Methyl 5,12-Bis(phenylmethoxy)-1,2,3,4,6,11-hexahydro-2-hydroxy-6,11-dioxonaphthacene-2-carboxylate (15)

A suspension of NaH (60 % dispersion in oil, 25 mg, 0.62 mmol) in THF (1 ml) was added to a solution of 6 (100 mg, 0.27 mmol) in THF (100 ml) at -78°C under Ar atmosphere and allowed to stand at room temperature. Tetra-*n*-butylammonium iodide (220 mg, 0.60 mmol) and benzyl bromide (0.5 ml, 4.2 mmol) were added to the reaction mixture and the whole was stirred under reflux for 5 h. After adding 10 % HCl (20 ml), the whole was extracted with ethyl acetate (20 ml x3). The combined organic layer was washed with 10 % HCl (20 ml), saturated NaHCO_3 (20 ml), brine (20 ml) and dried over MgSO_4 . Purification by silica gel column

chromatography (benzene-dichloromethane, 1/0 to 1/4) followed by recrystallization from benzene afforded 15 (137 mg, 92 %) as yellow prisms of mp 191°C. $[\alpha]_{D}^{25} +25^{\circ}$ ($c=0.12$, CHCl_3). IR (CHCl_3): 1730, 1670. $^1\text{H-NMR}$ (CDCl_3) δ : 1.8-2.0 (2H, m, CH_2), 2.9-3.0 (5H, m, CH_2OH), 3.80 (3H, s, CH_3O), 5.03 (4H, s, CH_2), 7.3-7.8 (12H, m, Ar), 8.2-8.3 (2H, m, Ar). MS m/z : 548 (M^+), 530 ($\text{M}^+ - \text{H}_2\text{O}$). Anal. calcd for $\text{C}_{34}\text{H}_{28}\text{O}_7$: C, 74.44; H, 5.14. Found: C, 74.28; H, 5.10.

(2*R*)-5,12-Bis(phenylmethoxy)-1,2,3,4,6,11-hexahydro-2-hydroxy-6,11-dioxonaphthacene-2-carboxylic acid (16)

3 % KOH (0.45 ml, 0.24 mmol) was added to a solution of 15 (93 mg, 0.17 mmol) in THF-MeOH (1:1, 4 ml) and the whole was stirred for 1 h. After adding 10 % HCl (5 ml), and the whole was extracted with ethyl acetate (20 ml x3) and washed with water (10 ml x3), brine (10 ml) and dried over MgSO_4 . Purification by silica gel column chromatography (dichloromethane-methanol, 8/1) afforded 16 (70 mg, 77 %) as a caramel. $[\alpha]_{D}^{25} -27^{\circ}$ ($c=0.55$, CHCl_3). IR (CHCl_3): 1670, 1720. $^1\text{H-NMR}$ (CDCl_3) δ : 1.8-2.1 (2H, m, CH_2), 2.7-3.1 (4H, m, CH_2), 5.00 (4H, s, CH_2), 6.1 (2H, brs, COOH , OH), 7.0-7.8 (12H, m, Ar), 8.0-8.2 (2H, m, Ar). MS m/z : 534 (M^+). HRMS Calcd for $\text{C}_{33}\text{H}_{26}\text{O}_7$: 534.1679. Found: 534.1631.

(8*R*)-6,11-Bis(phenylmethoxy)-7,8,9,10-tetrahydro-8-hydroxy-8-hydroxymethyl-5,12-naphthacenedione (17)

Diborane (1M in THF, 0.37 ml, 0.37 mmol) was added to a solution of 16 (20 mg, 0.037 mmol) in THF (2 ml) at 0°C and the reaction mixture was stirred for 4 h at room temperature. 10 % HCl (20 ml) was added to the mixture and the whole was stirred for 1 h at room temperature. After extraction with ethyl acetate (20 ml x3), the organic layer was washed with 10 % HCl (20 ml), satd. NaHCO_3 (20 ml), brine (20 ml) and dried over Na_2SO_4 . Purification by silica gel column chromatography (benzene-ethyl acetate, 3/1) afforded 17 (10 mg, 51 %) as yellow prisms of mp 170°C. $[\alpha]_{D}^{25} -37^{\circ}$ ($c=0.32$, CHCl_3). IR (CHCl_3): 1670, 1400. $^1\text{H-NMR}$ (CDCl_3) δ : 1.5-2.0 (2H, m, CH_2), 2.7-3.0 (5H, m, CH_2 , OH), 3.44 (1H, s, OH), 5.04 (4H, s, CH_2), 7.3-7.6 (10H, m, Ar), 7.7-7.8 (2H, m, Ar), 8.2-8.3 (2H, m, Ar). MS m/z : 521 (MH^+), 520 (M^+), 502 ($\text{M}^+ - \text{H}_2\text{O}$). HRMS Calcd for $\text{C}_{33}\text{H}_{28}\text{O}_6$: 520.1886. Found: 520.1906.

(8*R*)-7,8,9,10-Tetrahydro-6,8,11-trihydroxy-8-hydroxymethyl-5,12-naphthacenedione (9-Deacetyl-7-dehydroxy-4-demethoxy-9-hydroxymethyl-daunomycinone 5)

A mixture of 17 (5 mg) and palladium on carbon (10 %, 2 mg) in dioxane-ethanol (1:1, 2 ml) was stirred for 12 h at room temperature under hydrogen atmosphere. Filtration followed by purification with silica gel column chromatography (dichloromethane-acetone, 4:1) afforded 5 (2 mg, 61 %) as red prisms of mp 233-236°C. $[\alpha]_{D}^{25} -31^{\circ}$ ($c=0.20$, dioxane). [lit.^{3k} mp 235-238°C, $[\alpha]_{D}^{25} -32^{\circ}$ ($c=0.06$, dioxane).] IR (dioxane): 1630, 1590. $^1\text{H-NMR}$ (pyridine- d_5) δ : 2.0-2.5 (2H, m, CH_2), 3.0-4.0 (8H, m, CH_2 , OH, singlet at 4.02), 7.6-7.7 (2H, m, Ar), 8.3-8.4 (2H, m, Ar). MS m/z : 340 (M^+), 309 ($\text{M}^+ - \text{CH}_2\text{OH}$), 291 ($\text{M}^+ - \text{CH}_2\text{OH} - \text{H}_2\text{O}$). HRMS Calcd for $\text{C}_{19}\text{H}_{16}\text{O}_6$: 340.0947. Found: 340.0959.

(1*R*,2*R*)-2-Acetyl-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalene-1,2-diol (18)

To a cooled (-78°C) solution of the chiral diamine (-)-13 (98 mg, 0.21 mmol) in THF (10 ml) was added a solution of osmium tetroxide (48 mg, 0.19 mmol) in THF (1 ml). A solution of 11 (40 mg, 0.17 mmol) in THF

(1 ml) was added to the bright wine-red solution above at -110°C and the whole was stirred for 6 h at the same temperature. Sodium bisulfite (0.20 g) and water (4 ml) was added to the reaction mixture and the whole was stirred for 14 h under reflux. The reaction mixture was basified with NaHCO_3 and concentrated. The residue was suspended in ethyl acetate (50 ml) and filtered through Celite pad. The water layer of the filtrate was extracted with ethyl acetate (20 ml x2) and combined organic layer was washed with brine and dried over Na_2SO_4 . Concentration and the following purification by silica gel column chromatography (benzene-ethyl acetate, 10/1 to 1/1) gave chiral diamine 13 (94 mg, 96 %) and diol 18 (44 mg, 96 %) as a caramel of $[\alpha]_{\text{D}}^{25} -17.6^{\circ}$ ($c=1.10$, CHCl_3). IR (CHCl_3): 1710, 1600. $^1\text{H-NMR}$ (CDCl_3) δ : 1.7-2.1 (2H, m, CH_2), 2.39 (3H, s, CH_3CO), 3.7-3.9 (2H, m, CH_2), 3.8-4.0 (8H, m, CH_3O , and OH), 5.31 (1H, s, CH), 6.72 (2H, s, Ar). MS m/z : 267 (MH^+), 266 (M^+). HRMS Calcd for $\text{C}_{14}\text{H}_{18}\text{O}_5$: 266.1154. Found: 266.1174.

(2*R*,1'*R*) and (2*R*,1'*S*)-1,2,3,4-Tetrahydro-2-(1-hydroxyethyl)-5,8-dimethoxynaphthalen-2-ol (19)

A mixture of diol 18 (17 mg, 0.064 mmol), triethylsilane (0.14 ml, 0.088 mmol), and trifluoroacetic acid (0.7 ml) was stirred at -20°C for 12 h. Saturated NaHCO_3 (10 ml) and ethyl acetate was added to the mixture and the organic layer was washed with saturated NaHCO_3 and brine. After drying over Na_2SO_4 and concentration, the residue was purified by silica gel column chromatography (hexane-ethyl acetate, 3/1) to afford 19 (12.5 mg, 78 %) as a caramel. IR (CHCl_3): 3400-3450, 1600, 1480. $^1\text{H-NMR}$ (CDCl_3) δ : 1.25 (isomer: 1.27) (3H, d, $J=7\text{Hz}$, CH_3), 1.5-2.0 (5H, m, CH, CH_2 , OH), 2.5-2.9 (4H, m, CH_2), 3.77 (3H, s, CH_3O), 3.78 (3H, s, CH_3O), 6.63 (2H, s, Ar). MS m/z : 253 (MH^+), 252 (M^+). $^1\text{H-NMR}$ showed the ratio of isomers was 3:4.

(2*R*)-2-Acetyl-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalen-2-ol (8)

Triethylamine (0.32 ml, 2.3 mmol) and sulfur trioxide-pyridine complex (130 mg, 0.82 mmol) were added to a solution of diol 19 (20 mg, 0.080 mmol) in DMSO (0.2 ml). After adding 10 % HCl (10 ml) and ethyl acetate (50 ml), the organic layer was washed with 10 % HCl (10 ml), saturated NaHCO_3 (10 ml x2), brine and dried over Na_2SO_4 . Concentration followed by purification by silica gel column chromatography (benzene-ethyl acetate, 7/1) afforded 8 as colorless prisms (8.8 mg, 87 %) of mp $122-125^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{25} -39.3^{\circ}$ ($c=0.88$, CHCl_3) [82 %ee, lit.⁵ mp $128-129^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{25} -48.2^{\circ}$ ($c=0.982$, CHCl_3)]. IR (CHCl_3): 1710, 1490. $^1\text{H-NMR}$ (CDCl_3) δ : 1.8-2.1 (2H, m, CH_2), 2.30 (3H, s, CH_3CO), 3.61 (1H, s OH), 3.79 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.71 (2H, s, Ar). MS m/z : 251 (MH^+), 250 (M^+), 232 ($\text{M}^+-\text{H}_2\text{O}$).

3,4-Dihydro-5,8-dimethoxy-2-(1-methyl-2,5-dioxan-1-yl)naphthalene (12)

A mixture of ketone 8 (36 mg, 0.16 mmol), ethylene glycol (96 mg, 1.5 mmol) and *p*-toluenesulfonic acid (3 mg, 0.016 mmol) in benzene (15 ml) was stirred under reflux azeotropically for 12 h. The reaction mixture was diluted with ethyl acetate (40 ml) and washed with saturated NaHCO_3 (10 ml), water (20 ml x2), brine (20 ml) and dried over MgSO_4 . Concentration followed by purification by silica gel column chromatography (benzene) afforded 12 as a caramel (47 mg, 99 %). IR (CHCl_3): 1660, 1600. $^1\text{H-NMR}$ (CDCl_3) δ : 1.54 (3H, s CH_3), 2.1-2.3 (2H, m, CH_2), 3.78 (6H, s, OCH_3), 3.8-4.0 (4H, m, CH_2), 6.68 (2H, s, Ar), 6.98 (1H, s, CH). MS m/z : 276 (M^+). Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_4$: 276.1361. Found: 276.1384.

(1*S*,2*R*)-3,4-Dihydro-5,8-dimethoxy-2-(1-methyl-2,5-dioxan-1-yl)naphthalene-1,2-diol (20)

To a cooled (-78°C) solution of the chiral diamine (-)-13 (60 mg, 0.13 mmol) in THF (8 ml) was added a solution of osmium tetroxide (29 mg, 0.12 mmol) in THF (1 ml). A solution of 12 (29 mg, 0.11 mmol) in THF (2 ml) was added to the bright wine-red solution above at -110°C and the whole was stirred for 2 h at the same temperature and then 4 h at -78°C . Sodium bisulfite (1.0 g) and water (5 ml) was added to the reaction mixture and the whole was stirred for 12 h under reflux. The reaction mixture was basified with NaHCO_3 and concentrated. The residue was suspended in ethyl acetate (30 ml) and filtered through Celite pad. The water layer of the filtrate was extracted with ethyl acetate (10 ml x2) and combined organic layer was washed with brine and dried over Na_2SO_4 . Concentrated and purification by silica gel column chromatography (dichloromethane-ethyl acetate, 6/1) afforded diol 20 (25 mg, 77 %) as a caramel of $[\alpha]_{\text{D}}^{25} -24.5^{\circ}$ ($c=1.24$, CHCl_3). IR (CHCl_3): 3500, 1600. $^1\text{H-NMR}$ (CDCl_3) δ : 1.46 (3H, s, CH_3), 2.1-2.3 (2H, m, CH_2), 2.7-2.9 (2H, m, CH_2 , OH), 3.56 (1H, s, OH), 3.77 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 4.02 (4H, s, CH_2CH_2), 5.14 (1H, s, CH), 6.70 (2H, s, Ar). MS m/z : 311 (MH^+), 310 (M^+). HRMS Calcd for $\text{C}_{16}\text{H}_{22}\text{O}_6$: 310.1415. Found: 310.1410.

(2R)-2-Acetyl-1,2,3,4-tetrahydro-5,8-dimethoxynaphthalen-2-ol (18) from ketal 20

A solution of ketal 20 (19 mg) and 10 % HCl (0.4 ml) in THF (4 ml) was stirred for 2 d at room temperature. The mixture was diluted with ethyl acetate (90 ml) and washed with satd. NaHCO_3 (10 ml), brine (20 ml) and dried over Na_2SO_4 . Concentration followed by silica gel column chromatography (benzene-ethyl acetate, 10/1) gave 18 (14.3 mg, 88 %) as a caramel of $[\alpha]_{\text{D}}^{25} -7.7^{\circ}$ ($c=1.43$, CHCl_3). (36 %ee based on the optical rotation of Table 1 Run 2).

(8R)-8-Acetyl-7,8,9,10-tetrahydro-6,11,8-trihydroxy-5,12-naphthacenedione (4-Demethoxy-7-dehydroxydaunomycinone 4)

To a solution of 8 ($[\alpha]_{\text{D}}^{25} -39.3^{\circ}$ ($c=0.880$, CHCl_3), 82 % ee, 15 mg, 0.060 mmol) in nitrobenzene (2 ml) was added a solution of aluminum chloride (16 mg, 0.12 mmol) in nitrobenzene (0.5 ml) and the mixture was stirred for 30 min at room temperature. Phthaloyl dichloride (12 mg, 0.060 mmol) was added to the resulting orange solution and the whole was stirred at 100°C for 1 h. 0.2N oxalic acid (10 ml) and chloroform (30 ml) were added to the resulting purple solution and the whole was filtered through celite pad. The water layer was extracted with chloroform (10 ml x3) and the combined organic layer was washed with satd. NaHCO_3 (20 ml x2), brine (20 ml). After drying over MgSO_4 , concentration followed by silica gel column chromatography (benzene-dichloromethane, 1/3) afforded 4 (16 mg, 76 %) as red prisms of mp $209-215^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20} -73.0^{\circ}$ ($c=0.14$, CHCl_3), (81 %ee). Recrystallization from benzene (0.5 ml) gave red prisms (9.0 mg, 53 %) of mp $217-218^{\circ}\text{C}$. $[\alpha]_{\text{D}}^{20} -86.2^{\circ}$ ($c=0.10$, CHCl_3), ((96 %ee, lit.⁹ mp $218-219.5^{\circ}\text{C}$, $[\alpha]_{\text{D}}^{25} -90.6^{\circ}$ ($c=0.106$, CHCl_3)). IR (KBr): 3400, 1700, 1620. $^1\text{H-NMR}$ (CDCl_3) δ : 1.7-2.2 (2H, m, CH_2), 2.39 (3H, s, OCH_3), 2.8-3.5 (4H, m, CH_2), 3.80 (1H, s, OH), 7.7-7.9 (2H, m, Ar), 8.2-8.5 (2H, m, Ar), 13.49 (2H, s, ArOH). MS m/z : 352 (M^+), 309 ($\text{M}^+ - \text{COCH}_3$).

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Total Synthesis of (±)-4-Demethoxydaunomycinone†

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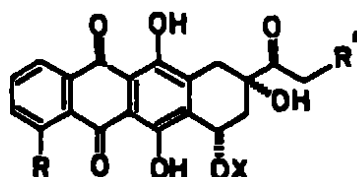
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2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (4), the key synthon for the total synthesis of various antitumor anthracyclines, has been prepared either from 1,4-dimethoxynaphthalene and making use of metal-ammonia reduction or from benzoquinone and going through Diels-Alder reaction with 1,3-butadiene. 4 is then converted into (±)-4-demethoxydaunomycinone (3b).

In the field of anthracyclines as anticancer agents¹, the synthetic analogue, 4-demethoxydaunomycin (3a) has assumed considerable clinical importance as it is found to be 8 to 10 times more effective than naturally occurring daunomycin (1a) or adriamycin (2a)². Further, 3a is orally active³. As there is no possibility of obtaining 3a by fermentation, and many suitable methods for the synthesis of L-daunosamine including two of our approaches⁴ either starting from glucose or glucosamine and its coupling to the aglycone (4-demethoxydaunomycinone, 3b), have already been accomplished⁵, our main efforts have been directed towards evolving a convenient synthesis of the aglycone (3b). Amongst several approaches⁶ towards the synthesis of both daunomycinone (1b) and 3b, the method first employed by Wong *et al.*⁷ for the assemblage of the tetracyclic system by AB + CD

coupling seems to be most promising. It involves the preparation of 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (4) representing the final AB rings and its condensation by acylation with phthalic anhydride corresponds to CD rings in the tetracyclic system. Various methods have since been reported for the synthesis of 4 which can be smoothly converted into 4-demethoxy-7-deoxydaunomycinone (5)⁸. We now report an efficient and a much simpler approach towards 4 employing easily accessible organic intermediates. Precise experimental procedures for the successful elaboration of such products have been outlined in view of their interesting application for the synthesis of other anthracyclines.

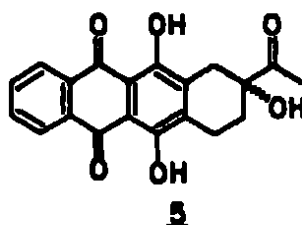
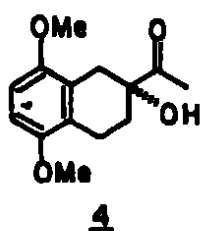
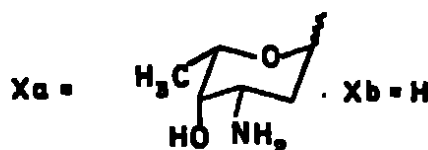
Our first approach for the synthesis of 4 was from 1,4-dimethoxynaphthalene (6) and used of metal-ammonia reduction as the key step as depicted in



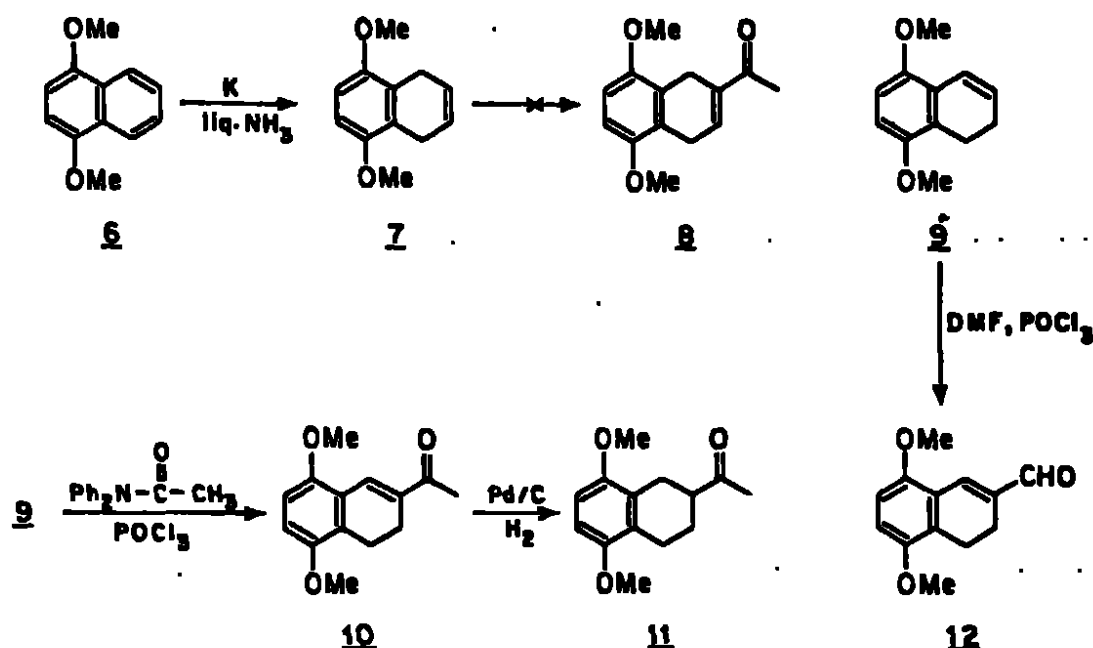
1 : R = OMe, R' = H

2 : R = OMe, R' = OH

3 : R = R' = H



†NCL Communication No. 3687



Scheme 1

Scheme 1. Thus metal-ammonia reduction of 6 either with lithium in liquid ammonia or lithium in ethylenediamine or potassium in ethylenediamine resulted in the recovery of starting material (in different gram atom equivalents). However, 6 on reduction with potassium in liquid ammonia, followed by quenching the reaction mixture with ethanol afforded 5,8-dimethoxy-1,4-dihydronaphthalene (7).

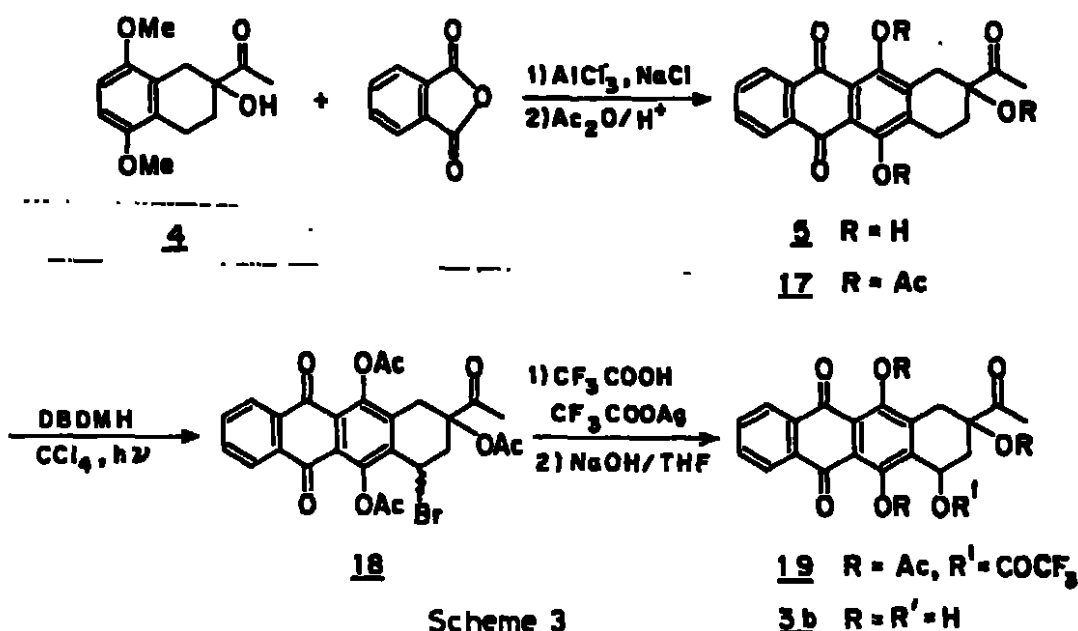
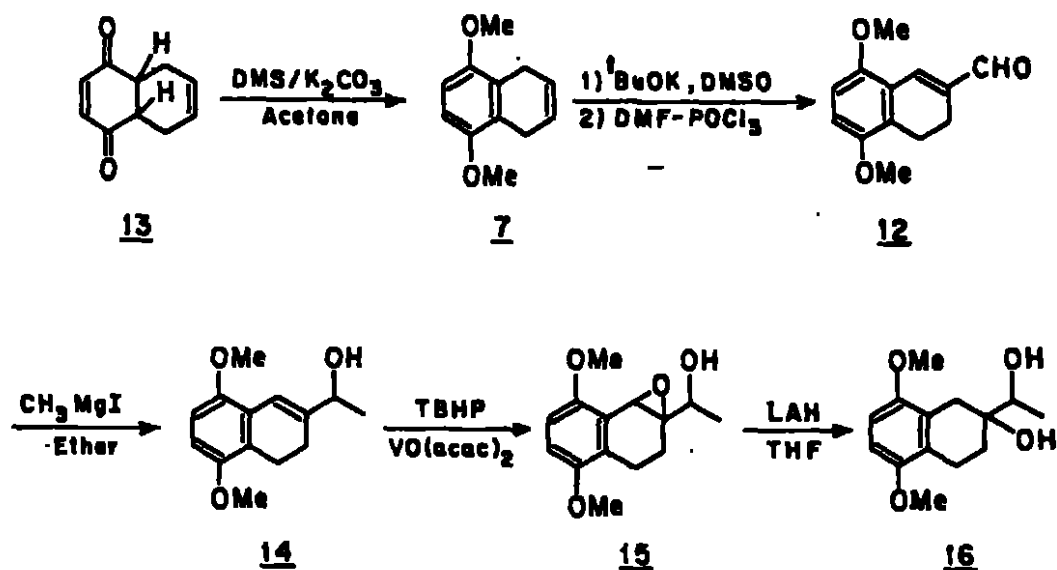
The various attempts to acylate the ethylenic double bond in 7 to achieve 8 (e.g. acetic anhydride-BF₃-etherate, acetic anhydride-AlCl₃, acetyl chloride-SnCl₄, acetyl chloride-ZnCl₂, acetic acid-PPA etc.) which could then be easily epoxidised and reductively opened to give the desired 4, resulted in a complex mixture. In view of this it was decided to isomerise the olefinic bond in 7 to the conjugated position as in 9 in the hope that 9 will be more prone to such acylation reactions. 7 on treatment with potassium *t*-butoxide in dimethyl sulphoxide under nitrogen atmosphere at room temperature resulted in the formation of 5,8-dimethoxy-3,4-dihydronaphthalene (9) in almost quantitative yield. After several unsuccessful attempts to acylate 9, it was found that using *N,N*-diphenylacetamide-phosphorous oxychloride in chloroform resulted in the formation of 2-acetyl-5,8-dimethoxy-3,4-dihydronaphthalene (10) in 10% yield. Attempts to improve the yield of 10 by varying the conditions of Vilsmeier-Haack reaction were unsuccessful. Catalytic hydrogenation of 10 using 5% Pd/C resulted in the formation of 2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (11) in 90% yield. Tertiary hydroxylation at C-2 position in 11 was achieved by treating 11 with potassium *t*-butoxide in *t*-butanol and bubbling oxygen followed by reduction

with zinc/acetic acid⁷ to give the desired ($\pm$)-2-acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (4) in 60% yield. It was evident that this approach is not suitable to obtain 4 in reasonable quantity.

Earlier it was demonstrated⁸ that 9 underwent formylation under Vilsmeier-Haack conditions using dimethylformamide and POCl₃ to give 2-formyl-5,8-dimethoxy-3,4-dihydronaphthalene (12) which could be smoothly transformed to 4 by appropriate reactions. However, 12 itself was obtainable through multistep operations⁹. This approach, therefore, was not attempted.

In yet another approach (Scheme 2) Diels-Alder reaction of *p*-benzoquinone with 1,3-butadiene in glacial acetic acid at room temperature afforded the adduct (13) in 90% yield. Methylation of 13 (Me₂SO, K₂CO₃-acetone method) afforded 5,8-dimethoxy-1,4-dihydronaphthalene (7) in 90% yield. This product was identical in all respects with that obtained by metal-ammonia reduction on 1,4-dimethoxynaphthalene (6). Base-catalysed isomerisation of 7 with potassium *t*-butoxide in DMSO afforded 9 in quantitative yield. Vilsmeier-Haack formylation (POCl₃-DMF, 80°) of 9 gave 12 in more than 90% yield. Grignard reaction on 12 with methylmagnesium iodide in ether afforded ($\pm$)-2-(1-hydroxyethyl)-5,8-dimethoxy-3,4-dihydronaphthalene (14) in 66% overall yield.

Epoxidation of 14 using *t*-butyl hydroperoxide, vanadyl acetylacetonate in benzene at room temperature followed by reduction with lithium aluminium hydride in tetrahydrofuran at room temperature afforded the vicinal diol (16). Fetizon oxidation¹⁰ of ($\pm$)-16 resulted in the formation of ($\pm$)-4 in very good yield. Further conversion of ($\pm$)-4 to 4

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demethoxydaunomycinone (3b) was achieved as depicted in Scheme 3.

Compound (4) was converted into 4-demethoxy-7-deoxydaunomycinone (5) in 70% yield^{8a}. The hydroxylation of the C-7 benzylic position in 5 was achieved by literature procedure via bromination of the corresponding triacetate (17), using 1,3-dibromo-5,5-dimethylhydantoin¹¹. Treatment of the bromo compound (18) with silver trifluoroacetate in trifluoroacetic acid at room temperature gave 19 in 30% yield. Various modifications made at this stage did not improve the yield of 19. Hydrolysis of 19 with sodium hydroxide in THF yielded (±)-4-demethoxydaunomycinone (3b) in 40% yield. The PMR and other spectral data of 3b are in complete agreement with the earlier reported data¹¹.

Thus the total synthesis of (±)-3b was accomplished by a practical and preparatively useful method.

Experimental Procedure

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer model 683 spectrophotometer and PMR spectra on either Varian T-60 or Varian FT-80 spectrometer (chemical shifts are given in δ scale) using TMS as an internal standard. Mass spectra were recorded on a CEC 21-110B mass spectrometer.

Analytical thin layer chromatography (TLC) was performed on (15 × 4 cm) glass plates with Acme's silica gel and visualization of the spots was achieved by exposure to iodine vapour. For column chromatography Acme's silica gel (60-120 mesh) was used. All

solvents and reagents were purified and dried by standard techniques.

(a) *5,8-Dimethoxy-1,4-dihydronaphthalene* (7)

To a stirred and cooled (-33°) solution of 1,4-dimethoxynaphthalene (6, 0.53 g, 2.8 mmol) in liquid ammonia (20 ml) was added potassium metal (0.672 g, 6 gram atom eq.) in portions during 10 min. After stirring for 30 min at 33° , the colour of the reaction mixture changed from blue to brown. Stirring was continued for further 3 hr at room temperature when most of the ammonia was evaporated. The reaction was quenched by adding absolute ethanol (25 ml) dropwise and stirred for 30 min. Ethanol was removed *in vacuo*, water (25 ml) added and extracted with chloroform. Evaporation of chloroform gave a gummy residue, which on chromatography over silica gel (benzene - hexane, 1:9) afforded pure 7 (0.213 g, 40%) as colourless needles, m.p. 53° (lit.¹² m.p. 50°); PMR (CCl_4): 3.20 (d, 4H, benzylic $-\text{CH}_2$), 3.73 (s, 6H, $2 \times \text{OCH}_3$), 5.80 (t, 2H, vinylic CH), 6.47 (s, 2H, aromatic); M^+ 190 (Found: C, 76.1; H, 7.5. Calc. for $\text{C}_{12}\text{H}_{14}\text{O}_2$: C, 75.8; H, 7.4%). Alternatively 7 was prepared in 90% from *p*-benzoquinone-butadiene adduct (13) as follows:

(b) To a solution of *p*-benzoquinone (54 g, 0.5 mol) in gl. acetic acid (500 ml) was introduced liquid butadiene (81 g, 1.5 mol) at 0° , the reaction mixture allowed to stand at room temperature for 36 hr, and poured over crushed ice with stirring. The colourless compound that precipitated was filtered and dried to obtain 13 (73 g, 90%).

A mixture of 13 (64.8 g, 0.4 mol), dimethyl sulphate (126 g, 1 mol) and potassium carbonate (200 g, 1.4 mol) in dry acetone (1 litre) was refluxed for 48 hr. Usual work-up afforded a solid which was crystallised from methanol to give 7 (68.3 g, 90%) as colourless needles, m.p. 51° (lit.¹² m.p. 50°).

5,8-Dimethoxy-3,4-dihydronaphthalene (9)

To a solution of 7 (0.57 g, 0.003 mol) in dry dimethyl sulphoxide (2.5 ml) was added potassium *t*-butoxide (40 mg, 0.00036 mol) and stirred under nitrogen at room temperature for 6 hr. The reaction mixture was poured over crushed ice and the solid separated was filtered, and crystallised from hexane to give 9 (0.56 g, 98%) as colourless plates, m.p. 70° , PMR (CCl_4): 2.2-2.7 (m, 4H, Hs on C-3 and C-4), 3.73 (s, 6H, $2 \times -\text{OCH}_3$), 5.93, 6.83 (m, 1H each, Hs on C-2 and C-1), 6.53 (s, 2H, aromatic); M^+ 190 (Found: C, 75.7; H, 7.4. $\text{C}_{12}\text{H}_{14}\text{O}_2$ requires C, 75.8; H, 7.4%).

2-Acetyl-5,8-dimethoxy-3,4-dihydro-naphthalene (10)

To a solution of 9 (0.95 g, 5 mmol) in chloroform (5 ml) was added a reagent (5 ml), prepared by mixing

N,N-diphenylacetamide (2.1 g, 10 mmol) and POCl_3 (1.61 g, 16.6 mmol) in chloroform (5 ml). The reaction mixture was refluxed for 4 hr, saturated aq. sodium acetate added and extracted with chloroform. Drying (Na_2SO_4) and evaporation of chloroform gave a gummy product, which on chromatography on silica gel (hexane - benzene 9:1), gave 10 (0.094 g, 10%) as yellow needles, m.p. 102° (lit.¹⁰ m.p. 104°); PMR (CDCl_3): 2.37 (s, 3H, COCH_3), 2.23-2.83 (m, 4H, $2 \times \text{CH}_2$), 3.76 (s, 3H, OCH_3), 3.83 (s, 3H, $-\text{OCH}_3$), 6.43, 6.66 (dd, $J = 8$ Hz, 2H aromatic), 7.60 (s, 1H, olefinic); M^+ 232 (Found: C, 72.1; H, 6.9. Calc. for $\text{C}_{14}\text{H}_{16}\text{O}_3$: C, 72.4; H, 6.8%).

2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (11)

A solution of 10 (1 g, 0.004 mol) in ethanol (25 ml) and 5% Pd/C (0.1 g) was hydrogenated at 20 psi and room temperature with mechanical shaking for 5 hr. The catalyst was filtered, washed with ethanol (10 ml) and the combined ethanol solution evaporated to dryness. The colourless residue was crystallised from ethanol-pet. ether (2:1) to give 11 (0.9 g, 90%), m.p. $81-82^{\circ}$ (lit.⁷ m.p. $81-82^{\circ}$); PMR (CDCl_3): 2.2 (s, 3H, COCH_3), 2.2-3.2 (m, 7H, $3 \times \text{CH}_2$ & CH), 3.73 (s, 6H, $2 \times \text{OCH}_3$), 6.46 (s, 2H, Ar-H); M^+ 234 (Found: C, 71.8; H, 7.7. Calc. for $\text{C}_{14}\text{H}_{18}\text{O}_3$: C, 71.8; H, 7.7%).

($\pm$)-*2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol* (4)

A solution of 11 (0.57 g, 2.45 mmol) in dry *t*-butyl alcohol (5 ml) was added to an oxygen saturated solution of potassium *t*-butoxide in *t*-butanol (45 ml). Dry oxygen was bubbled into the solution for 5 min, while keeping the reaction at 35° . The solution was cooled to 0° and glacial acetic acid added until it became acidic. Zinc dust (2 g) was immediately added and the solution stirred at room temperature for 6 hr. Zinc dust was filtered off and the filtrate concentrated on a rotary evaporator to give a residue which was diluted with water and extracted with chloroform. The chloroform layer was dried (Na_2SO_4), evaporated and the residue crystallised from methanol-ether to give 4 (0.6 g, 60%) as colourless needles, m.p. 99° (lit.^{8a} m.p. 97°); PMR (CDCl_3): 1.85 (t, 2H, C-3H), 2.3 (s, 3H, $-\text{COCH}_3$), 2.76 (t, 2H, Ar- CH_2), 2.8 (bs, 2H, Ar- CH_2), 3.4 (bs, 1H, $-\text{OH}$, D_2O exchangeable), 3.66 (s, 3H, $-\text{OCH}_3$), 3.73 (s, 3H, $-\text{OCH}_3$), 6.6 (s, 2H, Ar-H); IR (CHCl_3) 3200 (OH), 1685 cm^{-1} ($\text{C}=\text{O}$); M^+ 250 (Found: C, 67.0; H, 7.2. Calc. for $\text{C}_{14}\text{H}_{18}\text{O}_4$: C, 67.2; H, 7.2%).

5,8-Dimethoxy-3,4-dihydro-2-naphthaldehyde (12)

To a precooled (0°) solution of 9 (38 g, 0.2 mol) in dimethylformamide (80 ml) was added Vilsmeier-

Haack reagent prepared from POCl_3 (46 g, 0.3 mol) and DMF (36.5 g, 0.5 mol). The reaction mixture was heated at 80° for 3 hr and the hot solution poured over crushed ice. The solid that separated was filtered, washed with water, and dried and crystallised from methanol to give 12 (39 g, 90%) as light yellow plates, m.p. $91-92^\circ$ (lit.⁹ m.p. $91-92^\circ$); PMR (CCl_4): 2.03-2.90 (m, 4H, Hs on C-3 and C-4), 3.7 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 6.5 (dd, $J = 8$ Hz, 2H, Ar-H), 7.33 (t, 1H, vinylic H), 9.36 (s, 1H, aldehydic); M^+ 218 (Found: C, 71.6; H, 6.6. Calc. for $\text{C}_{13}\text{H}_{14}\text{O}_3$: C, 71.6; H, 6.4%).

2-(1-Hydroxyethyl)-5,8-dimethoxy-3,4-dihydronaphthalene (14)

To a solution of methylmagnesium iodide (60 ml, 35 g, 2.1 mol) in ether, a solution of 12 (21.8 g, 0.1 mol) in ether (600 ml) was added through a syringe under nitrogen at 10° and then stirred at room temperature for 1 hr. Saturated aluminium chloride solution (100 ml) was added and the mixture stirred for 20 min. The organic layer was separated, washed with water, dried (Na_2SO_4) and concentrated to give (±)-14 as a semisolid, which crystallised from, pet ether in colourless needles. (21.1 g, 90%), m.p. $78-79^\circ$ (lit.⁹ m.p. $78-79^\circ$); PMR (CDCl_3): 1.3 (d, $J = 6$ Hz, 3H, CH_3 -CHOH) 1.73 (bs, 1H, -OH, D_2O exchangeable), 2.06-2.36 (m, 2H, Hs on C-3), 2.56-2.86 (m, 2H, benzylic CH_2), 3.7 (s, 6H, $2 \times -\text{OCH}_3$), 4.1-4.5 (q, $J = 6$ Hz, 1H, - CH_3 -CH-OH), 6.43 (s, 2H, Ar-H), 6.53 (bs, 1H, vinylic H); M^+ 234 (Found: C, 71.9; H, 7.8. Calc. for $\text{C}_{14}\text{H}_{18}\text{O}_3$: C, 71.8; H, 7.7%).

2-Hydroxyethyl-2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene (16)

To a solution of 14 (4.68 g, 0.02 mol) in benzene (100 ml) was added vanadyl acetylacetonate (0.1 g, 0.003 mol) followed by *t*-butyl hydroperoxide (70%) (6 ml, 0.045 mol) at room temperature, and stirred for 4 hr. Benzene solution was washed with water and dried (Na_2SO_4). Removal of solvent on rotavapour gave 15 as a thick light brown gummy material which was subjected to LAH reduction as such.

To a solution of 15 in dry tetrahydrofuran (100 ml), LAH (1.14 g, 0.03 mol) was added in portions during 30 min and stirred for 3 hr. Saturated sodium carbonate solution was added at 0° and the contents were stirred for 30 min. The solid separated was filtered and washed with chloroform. The filtrate on evaporation of solvent gave a semisolid which was crystallised from benzene to give colourless needles of (±)-16 (3.53 g, 70%), m.p. 145° (lit.¹⁰ m.p. $145-46^\circ$); PMR (CDCl_3): 1.25 (d, $J = 6$ Hz, 3H, CH_3 -CHOH), 1.5-2.12 (m, 4H, 2H on C-3 and $2 \times \text{OH}$, after D_2O exchange integration reduced to half), 2.44-2.93 (m, 4H, Hs on C-1 and C-4), 3.75 (q, 1H merged with

methoxy groups, CH_3 -CH-OH), 3.75 (s, 3H, - OCH_3), 3.76 (s, 3H, OCH_3), 6.56 (s, 2H, Ar-H).

(±)-2-Acetyl-5,8-dimethoxy-1,2,3,4-tetrahydro-2-naphthol (4)

To the Fetizon reagent (20 g) (silver carbonate on celite powder) was added dry benzene (250 ml) and 16 (3 g, 0.012 mol). The contents were refluxed for 2 hr, filtered hot, benzene solution concentrated and passed over a column of silica gel with benzene as eluent to afford (±)-4, (1.8 g, 60%), m.p. 99° (lit.^{8a} 97° ; lit.¹⁰ $100-1^\circ$).

(±)-4-Demethoxy-7-deoxydaunomycinone (5)

An intimate mixture of 4 (0.25 g, 0.001 mol), phthalic anhydride (0.25 g, 0.0016 mol), aluminium chloride (2.5 g) and sodium chloride (0.5 g) was heated at 180° for 5 min. The resultant reddish mass was treated with a saturated solution of oxalic acid to give a red coloured solid, which was filtered, washed with water, dried and chromatographed on a silica gel column using 2% acetone in benzene as eluent to give (±)-5 (0.245 g, 70%) as reddish plates, m.p. $212-15^\circ$ (lit.¹³ m.p. $210-12^\circ$); PMR (CDCl_3): 1.96 (t, 2H, Hs on C-8), 2.36 (s, 3H, COCH_3), 3.03 (m, 4H, Hs on C-7 and C-10), 3.62 (s, 1H, OH, D_2O exchangeable), 7.78 (m, 2H, Ar-H), 8.26 (m, 2H, Ar-H), 13.27 (s, 2H, phenolic OH) (Found: C, 68.3; H, 4.7. Calc. for $\text{C}_{20}\text{H}_{16}\text{O}_6$: C, 68.2, H, 4.6%).

Acknowledgement

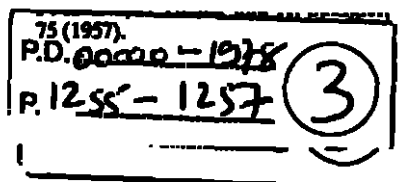
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Synthesis and antitumour activity of new daunorubicin and adriamycin analogues

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Summary. A new synthetic procedure for the preparation of daunorubicin and adriamycin analogues bearing different substituents on ring D, has been developed. The new compounds display outstanding efficacy against experimental tumours of mice.

Clinical usefulness of adriamycin (I) has prompted the study of new analogues of the antitumour anthracyclines with hopefully broader spectrum of activity and/or reduced cardiotoxicity^{1,2}. New derivatives modified in the C-9 side chain and in the sugar moiety have already excited pharmacological interest^{3,4}. However, it has recently been found that 4-demethoxydaunorubicin VIa and 4-demethoxyadriamycin VIIa, obtained by total synthesis of the aglycone moiety, according to Wong's synthetic sequence⁵, display a considerable antitumour activity on experimental tumours of laboratory animals^{7,8}.

Synthetic approaches to the daunomycinone system have been developed in different laboratories after the original synthesis of racemic 4-demethoxy-7-O-methyl-daunomycinone carried out by the Canadian authors⁶. These approaches include both Diels-Alder type reactions for the building of the tetracyclic chromophore^{9,10} as well as studies based on the Friedel and Crafts acylation of appropriate tetralines with phthalic acid derivatives¹¹⁻¹³. Racemic compounds were invariably obtained. Further developments have also been recorded in the glycosylation of the anthracyclines³.

A simplified synthetic procedure for optically active Va has been developed and is reported here. This procedure is

based on the direct formation of 7-deoxy-4-demethoxydaunomycinone IIIa by condensation of the optically active tetralin II with phthalic anhydride, a reaction which is accompanied by an outstanding preservation of the chiral centre, notwithstanding the harsh conditions employed. In the present communication, we also report on the antitumour activity of a group of new daunorubicin and adriamycin analogues (VI-f and VIIb) carrying different substituents on the aromatic ring and synthesized according to this general procedure.

Chemistry. (S)-(-)-6-acetyl-1,4-dimethoxy-6-hydroxytetralin¹⁴ (II, 4 g, 16 mmol), phthalic anhydride (4 g, 27 mmol), NaCl (8 g) and AlCl₃ (40 g) were thoroughly mixed and transferred into a flask immersed in an oil bath at 180 °C. The resulting melt was stirred for 2 min and after cooling the solid was treated with an excess of a saturated aqueous solution of oxalic acid. The suspension was extracted with chloroform and the extract was evaporated to give a residue which was taken up in ether to give 4 g (11.3 mmol) of IIIa, m.p. 228-230, [α]_D²⁰ -87° (c=0.1 CHCl₃), λ_{max} 460, 486, 520 nm (CHCl₃). This product was ketalized at C-13 with ethylene glycol (6 ml) in benzene (200 ml), in the presence of p-toluenesulphonic acid (0.2 g), for 5 h at reflux. The crude ketal was dissolved in a mixture

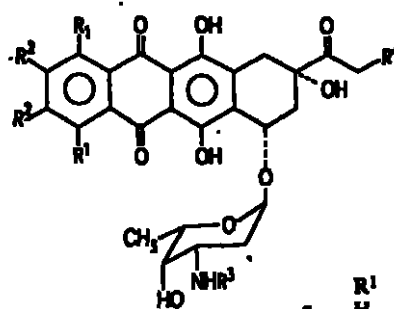
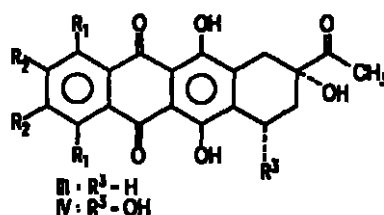
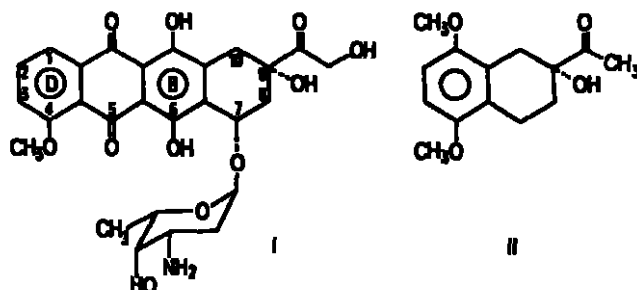
of chloroform (250 ml), carbon tetrachloride (100 ml) and water (200 ml), and treated at 80°C for 1 h with bromine (4 g) and 2,2'-azo-bis-isobutyronitrile (1 g). The organic layer was washed repeatedly, evaporated in vacuo, and the residue, mostly 4-demethoxy-7-epidaunomycinone, was treated overnight with trifluoroacetic acid and then with an excess of a 4% concentrated ammonium hydroxide in acetone to give, after chromatography on silicagel, 4-demethoxydaunomycinone⁷ (IVa), m.p. 184–186°, $[\alpha]_D^{20} +170^\circ$ (c=0.1 dioxane), $\lambda_{\max}$ 458, 484, 518 nm (CHCl₃) (1.2 g, 3.25 mmol).

The aglycone (1 g) and 2,3,6-trideoxy-3-trifluoroacetamido-4-O-trifluoroacetyl- α -L-lyxo-hexo-pyranosyl chloride¹³ (1.2 g) were dissolved in dichloromethane (150 ml), then silver triflate (1 g) in diethyl ether (20 ml) was added, in the dark and in 10 min, at room temperature. After 20 min, excess NaHCO₃ solution was added, the organic layer was evaporated, the residue was taken up in methanol (50 ml) and refluxed 30 min. Evaporation of the solvent left a residue that was chromatographed on a short silicagel column (chloroform/acetone ~ 95/5 as eluent) to give α -N-trifluoroacetyl-4-demethoxydaunorubicin (0.8 g)⁷ that was dissolved in 0.1 N NaOH (55 ml). After 30 min the solution was brought to pH 8 with HCl and extracted with chloroform. The solution was concentrated to 10 ml and methanolic HCl was added to pH 4.5. Addition of ether gave a red precipitate of 4-demethoxydaunorubicin hydrochloride⁷ (0.5 g).

This procedure, which greatly simplifies the synthesis of IVa, has been found suitable for the preparation of the analogues IVb, m.p. 208–210°, $\lambda_{\max}$ 460, 484, 518 nm; IVc, m.p. 143–145°, $\lambda_{\max}$ 464, 492, 526 nm; IVd, m.p. 195–197°, $\lambda_{\max}$ 474, 492, 528 nm; IVe, m.p. 160–162°, $\lambda_{\max}$ 478, 506, 542 nm; IVf, m.p. 185–187°, $\lambda_{\max}$ 467, 477, 511 nm. The condensation of the sterically hindered 3,6-dimethyl- and 3,6-dichlorophthalic anhydrides required somewhat higher temperatures and longer times and accordingly a small amount of racemic material was formed and could eventually be eliminated by crystallization, being less soluble than the optically active form. Since, however, it has already been proved¹⁶ that racemic 4-demethoxydaunomycinone could be clearly resolved through the condensation with 2,3,6-trideoxy-3-trifluoroacetamido-4-O-trifluoroacetyl- α -L-lyxo-hexo-pyranosyl chloride in the presence of silver triflate to the 7(S), 9(S)- α -glycoside and to the 7(R), 9(R)- β -glycoside, easily isolated in pure form by chromatography, it was found convenient to use this procedure with all the daunomycinone analogues synthesized, irrespective of their

optical purity. Subsequent chromatographic separation of the N-trifluoroacetyl- α -glycosides (Va-f) from the accompanying small amounts of 7(R), 9(R)- β -glycosides, followed by alkaline hydrolysis of the trifluoroacetamido group, yielded the optically pure daunorubicin analogues VIa-f. Conversion of VIb to VIIb was performed via bromination at C-14 and nucleophilic substitution of halogen with hydroxy group¹⁷. All compounds displayed chromatographic and spectroscopic properties consistent with the attributed structures.

Biological data. All substituted 4-demethoxydaunorubicins VIb-f displayed a high level of cytotoxic activity, although inferior to that of VIa (table). Similarly, VIIb appeared less effective than VIIa, but still more active than adriamycin itself. With the exception of the halogen-substituted compounds, all derivatives presented in the table displayed activity on L1210 leukemia in mice. In the daunorubicin series, compounds VIb and VIc appeared noteworthy, in addition to already known VIa, as regards to the antitumour efficacy in vivo. In the adriamycin series, outstanding antitumour properties were exhibited by VIIb, whose effect on the survival time of tumour-bearing animals was clearly superior to that of adriamycin. This compound was more effective than the corresponding daunorubicin analogue VIb. Derivatives VIb, VIc and VIe were also tested on P388 leukemia in mice in comparison with daunorubicin and VIa. Compound VIb was about twice as potent as daunorubicin, the 1,4-dimethyl analogue VIc appearing



	R ¹	R ²
a	H	H
b	H	CH ₃
c	H	Cl
d	CH ₃	H
e	Cl	H
f	H	-CH=CH-CH=CH-

Cytotoxic and antitumour activity of the new analogues compared with daunorubicin and adriamycin

Compound	Cytotoxicity ^a (EC ₅₀ , ng/ml)	L 1210 leukemia in mice ^b Dose ^c	AST ^d	P 388 leukemia in mice ^e Dose ^c	AST ^d
Daunorubicin	10.00	2.9	144	4.0	205
VIa	0.15	1.0	150	0.7	200
VIb	5.80	1.25	131	2.0	230
VIc	25.00	33.7	111		
VIe	10.05	6.6	147	10.0	165
VIe	7.15	20.0	116	22.5	140
VIe	27.00	10.0	135		
Adriamycin	15.00	2.9	141		
VIIa	0.10	0.5	166		
VIIb	7.00	4.4	173		

^a Inhibition of colony-forming ability of cultured HeLa cells after 24 h exposure to the drug. ^b Tumour inoculum 10⁵ cells, i.p.

^c Optimal doses, showing no toxicity (treatment i.p. on day 1, mg/kg of b. wt). ^d Average survival time expressed as percent of untreated controls. ^e Tumour inoculum 10⁵ cells, i.p.

instead less potent and less active than daunorubicin, V1a and V1b.

The biological properties of the new analogues indicate that considerable modification on ring D of the antitumour anthracyclines is compatible with the exhibition of antitumour efficacy. In particular, the 2,3-dimethyl-4-demethoxy analogue showed promising results in the animal tests.

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Naphthoquinone derivatives from the fungus *Hendersonula toruloides*

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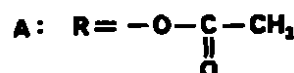
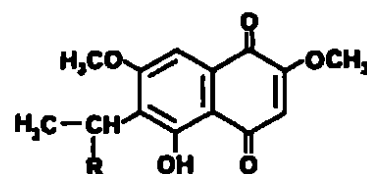
Summary. 2 yellow naphthoquinone derivatives were isolated from several pathogenic strains of *Hendersonula toruloides* Nattrass. They were identified as 2,7-dimethoxy-6-ethyl-5-hydroxy-1,4-naphthoquinone and 2,7-dimethoxy-5-hydroxy-6-(1-acetoxyethyl)-1,4-naphthoquinone by means of physico-chemical methods.

A fungus isolated from a patient (foot) was found to produce yellow crystalline material on malt agar. The fungus (CBS 131.78) was provided by M.K. Moore of St. John's Hospital for Diseases of the Skin in London and identified as *Hendersonula toruloides* Nattrass by G.A. de Vries of the Department of Medical Mycology of our institute. The strain M 56 (CBS 145.78-IMI 198935), one of several other isolates from patients supplied by C.K. Campbell of the M.R.C. Unit on the Experimental Pathology of the Skin in Birmingham, showed the same phenomenon as described above. TLC of an ethyl acetate extract of a culture of both strains revealed the presence of 2 yellow main pigments. Since only 1 pigment formed by *H. toruloides* has been described⁴, it was decided to investigate the nature of the 2 metabolites.

Each strain was grown on malt agar in 100 petri dishes for 20 days at 24 °C. Cultures were extracted with ethyl acetate. Purification was accomplished by means of column chromatography and preparative TLC using toluene/acetone (85:15, v/v) as the developing system. Merck silica gel 60 26×3 cm columns and Merck 2 mm silica gel thick-layer plates were used. Separation of the 2 pigments was successful on the silica gel plates.

Yellow bands comprising compound A, R_f 0.43-0.52 and compound B, R_f 0.53-0.63 were scraped off and eluted with chloroform/methanol (2:1, v/v). A and B were obtained as orange needles by twice recrystallizing from toluene/light petroleum 60-80 °C (1:1, v/v). A and B showed identical UV-visible spectra indicating the same chromophoric system for both pigments. The absorptions measured were similar to those described⁵ for the substance originally isolated from *H. toruloides*. Further study (MS, IR and PMR) revealed that B was identical with the known *Hendersonula* pigment, which was identified as 2,7-dimethoxy-

6-ethyl-5-hydroxy-1,4-naphthoquinone (2,7-dimethoxy-6-ethyljuglone, C₁₄H₁₄O₃). High resolution MS of A gave the formula C₁₆H₁₆O₇. Important peaks were observed at m/e 278 (M - CH₃CO) and m/e 260 (M - CH₃COOH). The IR-spectrum of A in CCl₄ compared with that of compound B



Formation of compounds A and B by other strains of *H. toruloides*

Strain No.	Origin	Yield mg/20 petri dishes	
		A	B
CBS 204.33	Plant	-	-
CBS 251.49	Plant	-	-
CBS 136.77	Man	1.4	0.4
CBS 137.77	Cow	10.4	1.7
CBS 661.77*	Man	-	-
CBS 662.77*	Man	0.2	-
M 38**	Man	-	-
M 48**	Man	0.2	0.9
M 52**	Man	-	-

* Isolates from M.K. Moore; ** isolates from C.K. Campbell.

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An Economical and Versatile Synthesis of 5,8-Dialkoxy-2-acetyl-3,4-dihydronaphthalenes: Key Precursors for the Synthesis of Chiral Anthracyclines

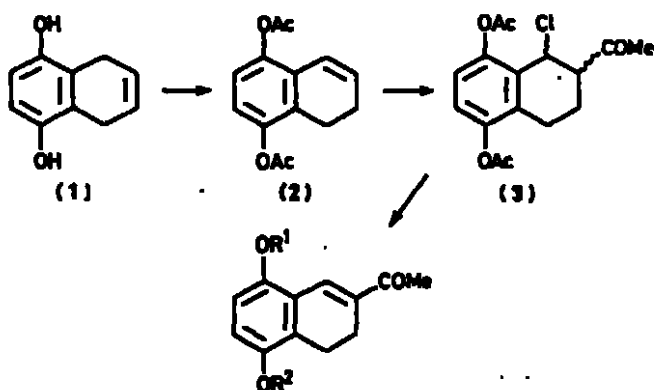
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5,8-Diacetoxy-2-acetyl-3,4-dihydronaphthalene, prepared by a new route from the Diels-Alder adduct of buta-1,3-diene and *p*-benzoquinone, is selectively deacetylated (Cs_2CO_3 in tetrahydrofuran or K_2CO_3 in dimethyl sulphoxide) to intermediates suitable for use in chiral anthracycline synthesis.

No short, cheap synthesis of the daunomycin group of anthracycline antineoplastic agents is yet available despite the continuing efforts of synthetic chemists. We¹ and others² have demonstrated that 5,8-dialkoxy-2-acetyl-3,4-dihydronaphthalenes [e.g. (5), (9), and (11)] are versatile intermediates useful as AB-synthons for the enantiospecific synthesis of anthracyclines. 5,8-Dialkoxy-2-acetyl-3,4-dihydronaphthalenes are



- (4) $\text{R}^1 = \text{R}^2 = \text{MeCO}$
 (5) $\text{R}^1 = \text{R}^2 = \text{Me}$
 (6) $\text{R}^1 = \text{H}, \text{R}^2 = \text{MeCO}$
 (7) $\text{R}^1 = \text{Me}, \text{R}^2 = \text{MeCO}$
 (8) $\text{R}^1 = \text{Me}, \text{R}^2 = \text{H}$
 (9) $\text{R}^1 = \text{Me}, \text{R}^2 = \text{CH}_2\text{Ph}$
 (10) $\text{R}^1 = \text{CH}_2\text{Ph}, \text{R}^2 = \text{MeCO}$
 (11) $\text{R}^1 = \text{CH}_2\text{Ph}, \text{R}^2 = \text{Me}$
 (12) $\text{R}^1 = \text{CH}_2\text{Ph}, \text{R}^2 = \text{H}$
 (13) $\text{R}^1 = \text{R}^2 = \text{H}$

presently available only by tedious multi-step sequences,³ which are unsuitable for large scale preparations. We now report a solution to this problem, which is short and uses simple reagents. Additionally, it allows discrimination between the C(5) and C(8) hydroxy groups of (13), a feature we have indicated previously,⁴ can be exploited to control regioselectivity in anthracycline syntheses.

5,8-Dihydroxy-1,4-dihydronaphthalene (1) is readily available in one step from benzoquinones and buta-1,3-diene.⁵ Under forcing conditions⁶ the double bond can be conjugated and the product recovered as the bisacetate (2). The addition of acetyl chloride, catalysed by AlCl_3 , forms a stereoisomeric mixture of the chloro-ketones (3) which, without purification, may be dehydrochlorinated by LiCl , to afford (4). Thus the basic skeleton is assembled in two operations, which is considerably shorter than any published route. Hydrolysis of (4),

Table 1

Starting compound	Product ^a	M.p./°C	Yield/%
(1)	(2)	137—138	53 ^b
(2)	(4)	148—150	90 ^b
(4)	(5)	103—104 ^c	65
(4)	(6)	171—173	62
(4)	(7)	157—158	55
(4)	(8)	201—203	80 ^b
(4)	(9)	111—112	65 ^b
(4)	(10)	131—132	57
(10)	(11)	132—134	65

^a All new compounds gave satisfactory combustion analyses and spectral data. ^b Optimised yields. ^c Lit.⁷ m.p. 104—105 °C.

† Complete conjugation of (1) (50 g) can be achieved by heating it in a solution of sodium hydroxide (150 g) and water (120 ml) at reflux under argon for 4 h.

followed by *in situ* methylation yields (5), a well-publicised intermediate³ in the enantiospecific and racemic synthesis of daunomycinone.

We examined next the mono-deacetylation of (4). Selective cleavage of the acetoxy group at C(8) occurred on treatment with caesium carbonate in tetrahydrofuran (THF)⁴ to afford (6). Anhydrous potassium carbonate in dimethyl sulphoxide⁵ was also successful and offered an economic advantage. Zinc catalysed methanolysis⁶ was unsuccessful.

The phenol (6) was methylated *in situ* to yield (7) which, in a single step could be further hydrolysed to (8), and benzylated to yield the ketone (9). The successful conversion of (4) to (9) was thus achieved in four steps.

2-Acetyl-8-benzyloxy-3,4-dihydro-5-methoxynaphthalene (11), the regioisomer of (9), was prepared in a similar way by reversal of the methylation-benzylation sequence. Isolation of the acetate (10) was necessary, prior to its hydrolysis to the phenol (12) and subsequent methylation.

The availability of the ketones (9) and (11), each by a simple process, renders these compounds good candidates for a large scale synthesis of (+)-daunomycinone.

† Monodeacetylation with K_2CO_3 is slow if THF is used as a solvent.

The realisation of such a synthesis together with the preparation of a variety of other chiral anthracyclines has been achieved⁴ and will be reported elsewhere.

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Novel Carrier Molecules for 'Up-hill' Transport of Metal Picrates

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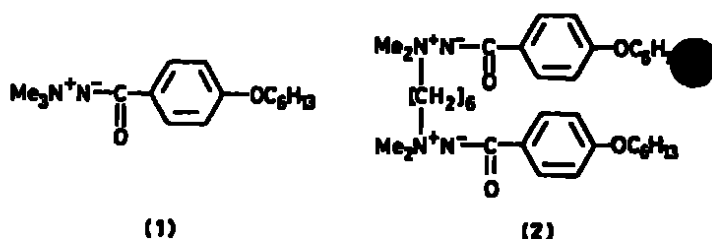
N-N Ylides have been synthesised for novel use as carrier molecules to transport metal picrates and organic anions through a liquid membrane; potassium picrate was successfully transported against its concentration gradient.

Metal ion transport across membranes is important in biology and is of great current interest.¹ Several functional carriers such as cyclic multidentate ligands or ionophores have been synthesised so as to mimic artificially the biological carriers.²⁻⁴

We report on an 'up-hill' transport system consisting of a liquid membrane containing an ylide as a novel carrier molecule. The ylides used here are carbonyl-stabilized aminimides, the electronic structures of which have been studied by X-ray photoelectron spectroscopy.^{5,7} The oxygen atom of the carbonyl group is conjugated to the anionic nitrogen in the aminimide and can bind to metal ions. The anionic nitrogen in the aminimides can also form a salt with HCl and so their electronic structures are affected by the concentration of protons in solution. We have been interested, then, in the aminimides as novel pH dependent carriers of metal ions and to compare the efficiency of such transport with that by the electrostatic field of the oxygen atoms of, for instance, crown ethers.

The aminimides could also be used as carriers for organic anions in that they possess a quaternary nitrogen atom.

The aminimides (1) and (2) were synthesized from the corresponding hydrazone salts. It is very important for the aminimide to have a long hydrocarbon chain as the concomitant insolubility in the aqueous phase protects the liquid membrane system from degradation. The structures of (1) and (2) were assigned from their i.r., n.m.r., and mass spectra and elemental analyses. For example, the $\nu(C=O)$ of (1) and (2) are 100 cm^{-1} lower than those of the corresponding



hydrazonium salts and downfield shifts were observed for the methyl hydrogen atoms of the aminimides from those of the hydrazine derivatives in their respective ^1H n.m.r. spectra. The pK_a values of the aminimides are 4.0–5.0, though the exact values can not be ascertained owing to the insolubility of (1) and (2) in water.

Participation of the carbonyl oxygens of the aminimides in the complexation of KClO_4 was shown by ^1H n.m.r. and Fourier transform (F.t.) i.r. spectroscopy. The addition of KClO_4 to $[\text{H}_4]$ methanol solutions of the aminimide caused significant changes in the chemical shifts of the methyl groups attached to the quaternary nitrogen [$\Delta\delta(\text{Me}_3\text{N}^+) = 0.10\text{ p.p.m.}$]. Furthermore, the carbonyl absorption in the F.t.-i.r. spectrum was broadened by the addition of KClO_4 to a methanol solution of the aminimide. The extraction of potassium ion by the aminimides was examined using the equilibrium of potassium picrate between an aqueous phase and a chloroform phase. Assuming that the complexation between metal picrate and aminimide was 1:1, the ion extrac-

United States Patent [19]

Arcamone et al.

[11] 4,077,988

[45] Mar. 7, 1978

[54] OPTICALLY ACTIVE
ANTHRACYCLINONES

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260/345.9 R; 424/331; 424/283[58] Field of Search 260/365, 383, DIG. 8,
260/376

[56] References Cited

U.S. PATENT DOCUMENTS

1,904,632 9/1975 Hollander 260/DIG. 8

OTHER PUBLICATIONS

Wong et al., ".....Daunomycinone" Canadian J. Chem. Canada, vol. 49, No. 16 (9/1971), pp. 2712-2718.

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[57] ABSTRACT

Disclosed are optically active anthracyclines and their daunosaminy derivatives, which are useful for the treatment of malignant diseases, particularly sarcomas, breast cancer, bronchogenic carcinoma, malignant lymphomas, neuroblastomas, acute leukemia and bladder cancer.

2 Claims, No Drawings

OPTICALLY ACTIVE ANTHRACYCLINONES

CROSS-REFERENCE TO RELATED APPLICATION

This application is related to and incorporates by reference the entire contents of applications, Ser. No. 560,105 (now U.S. Pat. No. 4,039,663), 568,437 (now abandoned) and 579,901 (now U.S. Pat. No. 4,046,878), filed respectively on Mar. 19, 1975; Apr. 16, 1975; and May 22, 1975, all of which are owned by the assignee hereof.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates to certain novel optically active anthracyclinones of the daunomycin group, daunosaminyl derivatives of said compounds and methods for the preparation thereof.

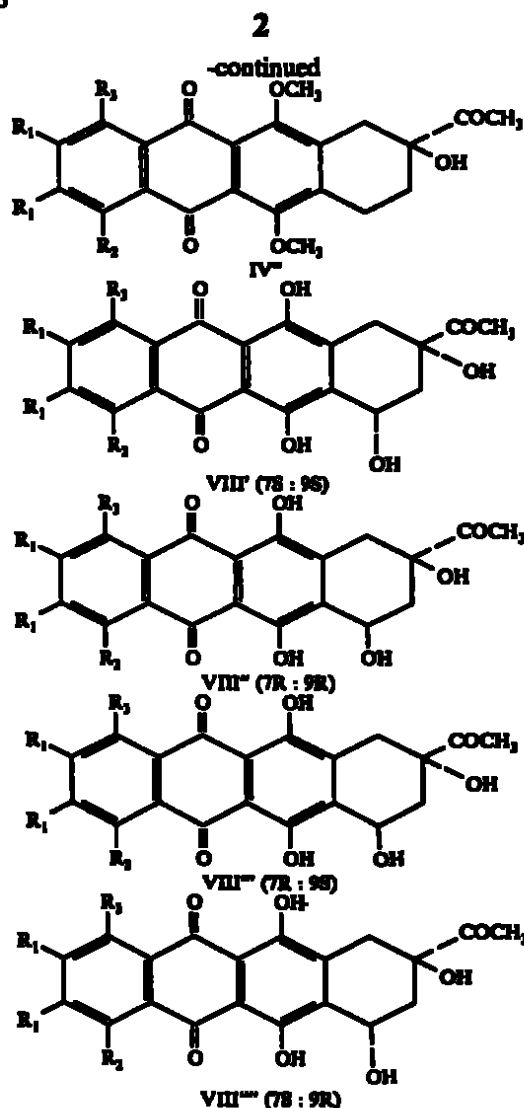
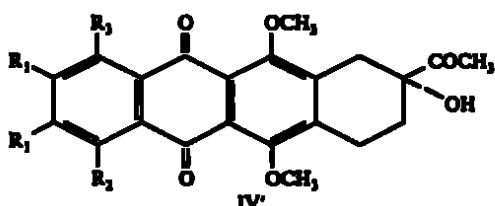
2. The Prior Art

While the optically active anthracyclinones of the invention are novel, the corresponding racemates of certain of them have been described in the literature; see C. M. Wong et al, *Canad. J. Chem.*, 49, 2712 (1971) and *Canad. J. Chem.*, 51, 466 (1973).

SUMMARY OF THE INVENTION

The present invention, in one aspect thereof, relates to a novel class of optically active anthracyclinones of the daunomycin group and to the daunosaminyl derivatives thereof. In another aspect, the invention relates to methods for the preparation of such compounds.

These compounds are useful for the treatment of malignant diseases, particularly sarcomas, breast cancer, bronchogenic carcinoma, malignant lymphomas, neuroblastomas, acute leukemia and bladder cancer. The novel anthracyclinones of the invention are optically active compounds of the general formulae IV', IV'', VIII', VIII'', VIII''' and VIII''':



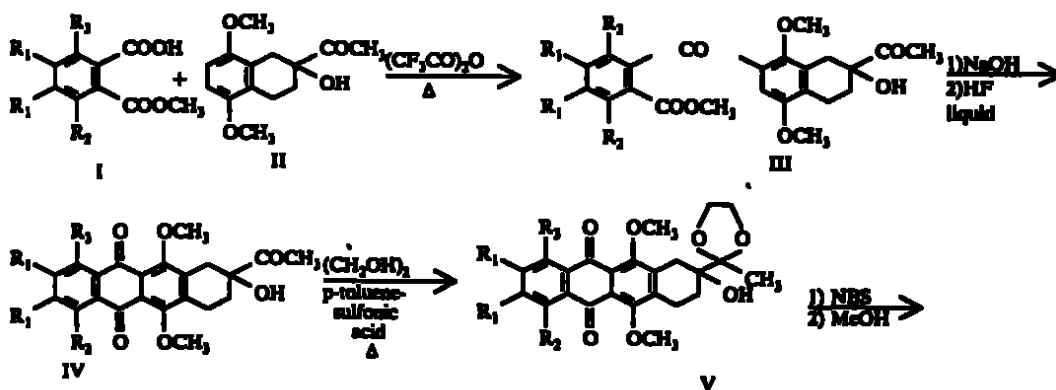
wherein

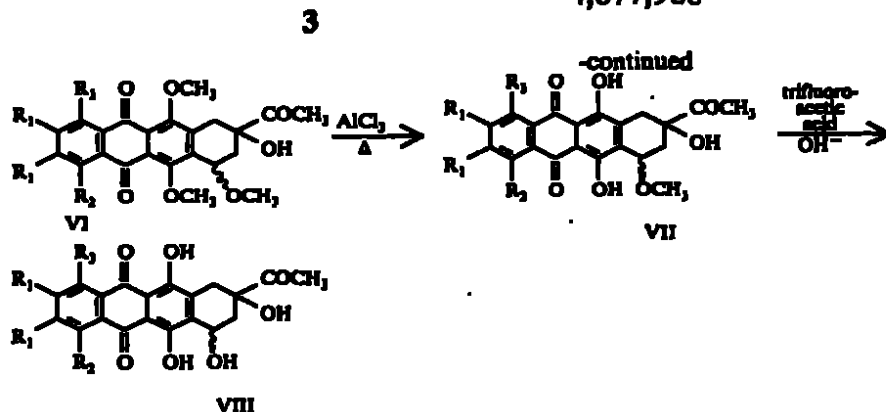
(a) R₁ is hydrogen and R₂ and R₃ are the same and are hydrogen, methyl, methoxy, chlorine or bromine;

(b) R₂ and R₃ are both hydrogen and R₁ is methyl, methoxy, chlorine or bromine; or

(c) R₁ and R₂ are both hydrogen and R₃ is methoxy.

The above optically active anthracyclinones of the formulae IV', IV'', VII', VII'', VIII''' and VIII''' are themselves novel, although some of the corresponding racemates have been described by C. M. Wong et al, *supra*. The synthesis of the racemates as described by Wong et al proceeds according to the reaction scheme:





The above reaction scheme yields anthracyclinones of the general formula VIII in the racemic form, whereas the natural aglycones are optically active and have the 7S : 9S configuration (according to the nomenclature of Cahn, et al, *Experientia*, 1956, 12, 81).

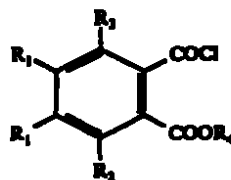
In order to obtain the natural anthracycline antibiotics and/or their analogues substituted in ring D by condensation of the aglycones with an appropriate derivative of daunosamine according to applications Ser. Nos. 568,437, filed Apr. 16, 1975 (now abandoned) and 579,901, filed May 22, 1975 (now U.S. Pat. No. 4,046,878), it would therefore be preferable to employ optically active aglycones having the 7S : 9S configuration rather than condensing the daunosamine derivative with the racemic aglycone and subsequently separating the (-)-daunosaminy (-)-anthracyclinone from the (-)-daunosaminy (+)-anthracyclinone, by a troublesome and time consuming procedure such as fractional crystallization or chromatography.

It is known (Eliel, *Stereochemistry of Carbon Compounds*, page 55, — McGraw-Hill, 1962) that the optical resolution of alcohols can be carried out in the best manner through a salt formation of the hemiphthalates with an optically active base. However, the poor solubility of the anthracyclinones VIII and their derivatives in most solvents makes this procedure practically useless. Moreover, from a practical and economical point of view the resolution should be performed at the earliest possible stage in the overall synthesis in order to perform the synthetic procedure on the optically active intermediate already having the required configuration. The first intermediate having the necessary chiral center is the ketol derivative II. Prior to this invention, no method was known for the optical resolution of such a derivative.

This invention accordingly provides a novel process for the optical resolution of a ketol having the general formula II herein, which comprises reacting (-)-1-phenyl-ethylamine with racemic 1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin in a suitable solvent such as acetonitrile to give the diastereoisomeric Schiff bases which are separated by crystallization and from which the enantiomeric ketols II are recovered by acid treatment. The separation is clean-cut and totally unexpected since no previous cases of the resolution of ketones via ketimines have been reported (Eliel, loc. cit., page 56); most probably because Schiff bases are usually rather unstable and decompose easily during crystallization. Moreover, it has now been found that the optically active ketols II can be reconverted into the racemic ketol II and it is therefore possible to convert the racemic ketol II into the required optically active form in very high yield, via the resolution of the racemic keton II with (-)-1-phenyl-ethylamine followed by the reconversion of the

unwanted isomer back into the racemic form, and repetition of the optical resolution.

The above reaction scheme proposed by Wong et al, employs, in several of the reaction steps, strongly acidic conditions which favor the racemization of the chiral center via a planar carbocation (Eliel, loc. cit., page 372); and in fact, operating as described by Wong et al on optically active ketol II, the resulting anthraquinone IV is completely devoid of optical activity. The present invention accordingly provides a novel method of synthesizing of the optically active compounds IV' and IV'' which comprises condensing an optically active ketol II with an appropriate phthalic acid monoester monochloride of the general formula I':



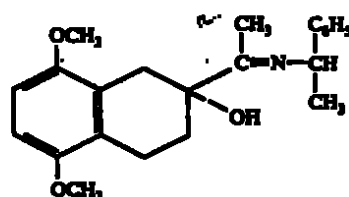
wherein R₁, R₂ and R₃ are as defined above, and R₄ is methyl, ethyl or halosubstituted ethyl, in the presence of a Lewis acid such as anhydrous aluminum chloride in a suitable solvent such as carbon disulphide, dichloromethane, tetrachloroethane, benzene or nitrobenzene to give, after treatment with sodium hydroxide, an optically active benzoyl benzoic acid III. Compound III is then cyclized to the corresponding optically active compound IV' or IV'' with liquid hydrogen fluoride or with methanesulphonic acid/P₂O₅. The reagent methanesulphonic acid/P₂O₅ is disclosed in *J. Org. Chem.*, 38, 4071, (1973).

In view of the easy racemization of the ketol chiral center, the isolation of compounds IV' and IV'' in optically active form is quite unexpected.

The optically active compounds IV' and IV'' can surprisingly be converted, according to the invention, into the optically active forms of the ketal V without racemization, by treatment with ethylene glycol in the presence of p-toluenesulphonic acid at elevated temperatures. Treatment of the optically active ketal V with N-bromo-succinimide in carbon tetrachloride gives a labile 7-bromo-ketal, which on treatment with methanol, yields a mixture of 7(S) and 7(R) methyl ethers. These methyl ethers may be demethylated at the 6- and 11-positions by treating same with an aluminum halide, such as aluminum chloride or bromide in a homogeneous solution in chlorobenzene, bromobenzene or nitrobenzene, preferably, nitrobenzene, to produce the

demethylated compounds in high yield and in a single step. The amount of aluminum halide used is not critical and can be from 1 to 20 moles per mole of the methyl ether compound, but the best results are obtained with 4-8 moles of aluminum halide. The temperature at which the reaction is conducted can be varied from 0° to 50° C., but the best results are obtained at temperatures of 20° C. or less. This procedure is disclosed in greater detail in U.S. Pat. No. 3,963,760 which corresponds to British Patent No. 1461190. Using this technique, the optical activity of the demethylated compounds is retained; thus there is obtained a mixture of 7(S)- and 7(R)-methoxy-anthracyclones which is then treated with trifluoroacetic acid and subsequently with sodium bicarbonate to give the corresponding 7(S)- and 7(R)-hydroxy derivatives. These latter are separated by crystallization or by chromatography on silica gel to give the appropriate optically active pure compounds VIII' (7S : 9S configuration), VIII'' (7R : 9R configuration) and their 7-epimers, that is VIII''' (7R : 9S configuration) and VIII'''' (7S : 9R configuration) in which R₁, R₂ and R₃ are as defined above. The compounds VIII' to VIII'''' are novel compounds that are provided by the present invention.

A preparation of the optically active anthracyclones VIII' according to the invention is described below in greater detail by way of example. The racemic ketol II is condensed with (-)-1-phenylethylamine in a suitable aprotic solvent such as acetonitrile to give a crystalline Schiff base IX.

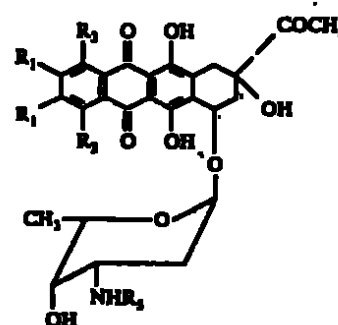
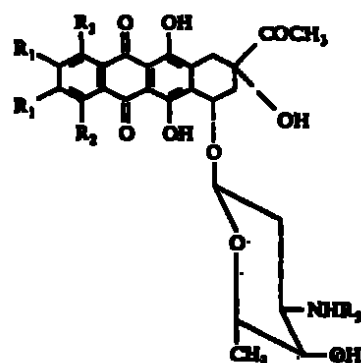
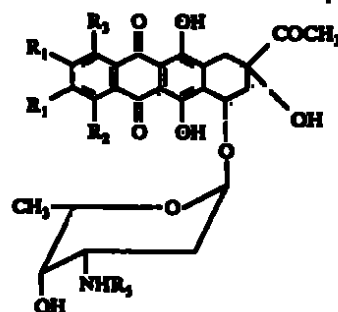


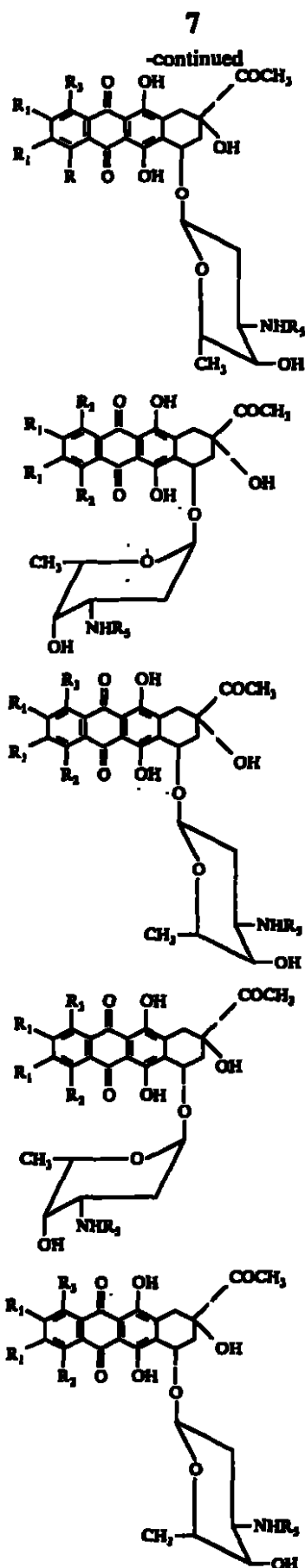
and mother liquors from which, by treatment with dilute acid, the (-) and (+) forms of the ketol II are isolated.

The (-) form of the ketol II is then condensed with an appropriate phthalic acid monoester monochloride in a suitable solvent such as carbon disulphide, dichloromethane, tetrachloroethane, nitrobenzene or benzene in the presence of aluminum trichloride or another Lewis acid to give the corresponding optically active benzoyl benzoate III. This compound III is hydrolyzed with alcoholic sodium hydroxide and the resulting acid is then treated with liquid hydrogen fluoride at a temperature of 0° to 25° C. for 3 to 10 hours or with methanesulphonic acid/P₂O₅ reagent at 25° C. for 24 hours. The resulting anthraquinone IV' is then treated with diethylene glycol in benzene or ethylene tetrachloride in the presence of a trace of a strong acid such as toluene-sulphonic acid in an apparatus provided with a trap to collect the water formed in the reaction, to give the corresponding optically active ketal V which is then irradiated with a tungsten lamp at reflux in carbon tetrachloride with N-bromo-succinimide for 5 to 15 minutes to give the labile 7-bromoketal. The latter compound is not isolated, and is treated with methanol to yield a mixture of 7(S) and 7(R) methyl ethers VI. This mixture (without purification) is reacted with aluminum chloride in benzene, nitrobenzene or tetrachloroethane at between 5° and 50° C. for 1 to 10 hours to give a mixture of 7(S) and 7(R) methoxy-anthracyclones VII. Treat-

ment of VII with trifluoroacetic acid at 5° to 30° C. for 8 to 20 hours and subsequently with sodium bicarbonate for a short time gives anthracyclones of formula VIII' together with their 7(R) epimers that are separated by crystallization or chromatography to give pure VIII' (cis 7,9 diol diastereomer). The 7(R)-epimer VIII''' (trans 7,9 diol diastereomer) is isolated and eventually recycled together with VII for the trifluoroacetic acid treatment. Similarly, from the (+) form of the ketol II, operating as above, the compound VIII'' (7R : 9R configuration) and its 7(S)-epimer VIII'''' (7S : 9R configuration) can finally be obtained.

The invention also provides a process for the synthesis of a compound X, X', XI, XI', XII, XII', XIII and XIII' in which R₁, R₂ and R₃ are as defined above and R₄ is H or COCF₃. The compounds X, X', XI, XI', XII, XII', XIII and XIII' are also novel compounds provided by the invention.





The process for making these latter compounds comprises condensing 2,3,6-trideoxy-3-trifluoroacetamido-

4-O-trifluoroacetyl- α -L-lyxopyranosyl chloride as described in application Ser. No. 560,105, filed Mar. 19, 1975 (now U.S. Pat. No. 4,039,663, with an appropriate optically active anthracycline VIII' to VIII''' in an anhydrous solvent in the presence of HgO, HgBr₂, and a molecular sieve, or condensing 1,2,3,6-tetradeoxy-4-O-trifluoroacetyl-3-trifluoroacetamido-L-lyxo-hex-1-enopyranose, as described in application Ser. No. 568,437, filed Apr. 16, 1975 (now abandoned), with an appropriate optically active anthracycline VIII' to VIII''' in an anhydrous solvent such as benzene or nitromethane in the presence of *p*-toluenesulphonic acid, and treating the resulting 7-(4'-O-trifluoroacetyl-3'-trifluoroacetamido-L-lyxo-pyranosyl-) intermediates first with methanol to obtain the corresponding N-trifluoroacetyl derivatives X, X', XI, XI', XII, XII', XIII, XIII' wherein R₃ is COCF₃, which are isolated as such or are treated successively with 0.1 N NaOH for 30 minutes at room temperature to eliminate the last trifluoroacetyl protecting group on the sugar moiety to thereby finally obtain the desired end products.

In the preparative examples which follow, references to daunomycinones are intended to mean anthracyclineones which have the same configuration (7S : 9S) as natural daunomycinone, and references to 7,9-bis-epi-daunomycinones are intended to mean anthracyclineones with the 7R : 9R configuration. The products of the Examples are novel compounds with the exception of daunomycinone itself.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention will now be described in greater detail in conjunction with the following examples which are not intended to be a limitation of the invention. All parts given are by weight unless otherwise indicated.

EXAMPLE 1

Resolution of 1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin.

13.8 gm. of 1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin in 50 ml. of acetonitrile and 7.4 gm. of (-)-1-phenylethylamine were heated for 5 min. at 80° C. The solution was slowly cooled to room temperature, and after 3 hrs. the crystalline precipitate was collected (6 gm.; m.p. 190°-192°; $[\alpha]_D^{20} - 38^\circ$, *c* = 1, CHCl₃) and dissolved in 50 ml. of methanol containing 12 ml. of 2 N HCl. The solution was heated at 50° for 10 min., then diluted with water and extracted with chloroform. The chloroform extract was evaporated in vacuo and the residue crystallized from chloroform-ethyl ether to give (-)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin (II) (4.3 gm.; m.p. 130°-132°; $[\alpha]_D^{20} - 50^\circ$, *c* = 1, CHCl₃).

The acetonitrile mother liquors were evaporated in vacuo and the residue taken up in 50 ml. of methanol containing 14 ml. of 2 N HCl. The solution was heated at 50° for 10 min., then diluted with water and extracted with chloroform. The chloroform extract was evaporated in vacuo and the residue crystallized from chloroform-ethyl ether to give (+)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin (4.8 gm; m.p. 130°-132°; $[\alpha]_D^{20} + 50^\circ$, *c* = 1, CHCl₃). From the mother liquors 4.5 gm. of racemic 1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin were recovered by concentration and recycled.

EXAMPLE 2

4-Demethoxy-7-desoxy-daunomycinone dimethyl ether (IV'; $R_1=R_2=R_3=H$).

To 5 gm. of (-)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin in 50 ml. of dichloromethane, 20 gm. of phthalic acid methyl ester monochloride were added and, over a period of 1 hour, 15 gm. of $AlCl_3$ were slowly added thereto with constant stirring at room temperature. The suspension was kept at room temperature for 2 hrs. and then poured onto ice.

The solution was extracted with chloroform and the extracts washed with water and with dilute $NaHCO_3$ solution. The chloroform extracts were evaporated in vacuo and the oily residue was taken up in 100 ml. of 60% ethanol containing 8 gm. of $NaOH$. The solution was kept at 60° for one hour, then diluted with water and extracted with chloroform. By evaporation of the chloroform extracts, (-)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin (0.6 gm.; m.p. 130°-132°; $[\alpha]_D^{20} - 50^\circ$, $c = 1$, $CHCl_3$) was recovered and recycled. The aqueous solution was acidified with 2 N HCl and extracted with chloroform. Evaporation of the solvent leaves an oily residue (III; $R_1=R_2=R_3=H$; 9 gm.) that was dissolved in 20 ml. of liquid HF . After 3 hrs. the HF was evaporated and the residue taken up in chloroform. The chloroform extract was washed with water and 2 N $NaOH$ and then evaporated in vacuo. The residue was crystallized from ether to give 4.9 gm. of 4-demethoxy-7-desoxy-daunomycinone dimethyl ether (IV'; $R_1=R_2=R_3=H$; m.p. 142°-144°; $[\alpha]_D^{20} - 33^\circ$; $c = 1$, $CHCl_3$).

EXAMPLE 3

4-Demethoxy-7-desoxy-9-epi-daunomycinone dimethyl ether (IV''; $R_1=R_2=R_3=H$).

Operating as in Example 2, but employing (+)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin, there was obtained 4-demethoxy-7-desoxy-9-epi-daunomycinone dimethyl ether (m.p. 142°-144°; $[\alpha]_D^{20} + 34^\circ$; $c = 1$, $CHCl_3$).

EXAMPLE 4

4-Demethoxy-7-desoxy-7-methoxy-daunomycinone (VII; configuration 9S; $R_1=R_2=R_3=H$).

5 gm. of 4-demethoxy-7-desoxy-daunomycinone dimethyl ether dissolved in 500 ml. of benzene containing 10 ml. of ethylene glycol and 0.3 gm. of p-toluenesulfonic acid were refluxed in a Dean-Stark apparatus for 5 hrs. The solution was cooled, 0.5 ml. of pyridine was added, and the solution washed with water. Evaporation of the solvent leaves a residue that is crystallized from ether to give 5 gm. of the ketal V (configuration 9S; $R_1=R_2=R_3=H$; m.p. 175°-177°; $[\alpha]_D^{20} - 29^\circ$, $c = 1$, $CHCl_3$). This product was dissolved in 300 ml. of CCl_4 containing 2.5 gm. of N-bromosuccinimide. The solution was heated at reflux for 10 minutes using a 500 watt tungsten lamp. After cooling, the solution was evaporated in vacuo and the residue taken up in 200 ml. of methanol and refluxed for 5 hrs. After evaporation of the solvent, the residue was taken up in 150 ml. of dioxane containing 60 ml. of water and 20 ml. of concentrated HCl . The solution was kept overnight at room temperature, then concentrated in vacuo. The residue was taken up in chloroform, which was washed with water and 5% $NaHCO_3$, and re-evaporated in vacuo to give 4.8 gm. of raw VI (configuration 9S) as a mixture

of the 7(S) and 7(R) epimers. This residue was dissolved in 400 ml. of benzene. 8 gm. of $AlCl_3$ were added and the suspension stirred for 2 hrs. at 40°. The solution was cooled, 1050 ml. of 3% oxalic acid were added and chloroform was added to complete solution. The organic layer was washed with water and 5% $NaHCO_3$ and evaporated to dryness. The residue was chromatographed on silica gel. Upon elution with chloroform, 2.8 gm. of 4-demethoxy-7-desoxy-7-methoxy-daunomycinone (VII, configuration 9S; $R_1=R_2=R_3=H$), as a mixture of the 7(S) and 7(R) epimers, were collected and used, as such in the following example. The pure 7(S) isomer can be obtained by careful chromatography, m.p. 155°-157°; $[\alpha]_D^{20} + 145^\circ$, $c = 0.1$, dioxane.

EXAMPLE 5

4-Demethoxy-daunomycinone (VIII'; $R_1=R_2=R_3=H$).

1.5 gm. of a mixture of the 7(S) and 7(R) epimers of 4-demethoxy-7-desoxy-7-methoxy-daunomycinone (VII, configuration 9S; $R_1=R_2=R_3=H$) prepared as in Example 4 were dissolved in 60 ml. of trifluoroacetic acid and left overnight at room temperature. The solution was evaporated in vacuo, the residue taken up in 150 ml. of acetone and 60 ml. of 5% $NaHCO_3$ were added. The solution was left at room temperature for 30 minutes, then diluted with water and extracted repeatedly with chloroform. Evaporation of the solvent left a residue that was chromatographed on silica gel. On elution with chloroform, 0.6 gm. of 4-demethoxy-daunomycinone (VIII', $R_1=R_2=R_3=H$; m.p. 185°-187°; $[\alpha]_D^{20} + 165^\circ$, $c = 0.1$, dioxane) and 0.5 gm. of 4-demethoxy-7-epi-daunomycinone (VIII''; $R_1=R_2=R_3=H$; $[\alpha]_D^{20} - 86^\circ$; ($c = 0.1$, dioxane) were collected.

EXAMPLE 6

4-Demethoxy-daunomycinone (VIII'; $R_1=R_2=R_3=H$).

When 4-demethoxy-7-epi-daunomycinone (Example 5) was treated with trifluoroacetic acid in the manner reported in Example 5 for 4-demethoxy-7-desoxy-7-methoxy-daunomycinone, there was obtained 4-demethoxy-daunomycinone in 48% yield.

EXAMPLE 7

4-Demethoxy-7,9-bis-epi-daunomycinone (VIII''; $R_1=R_2=R_3=H$).

Operating as in Examples 4 and 5, but employing 4-demethoxy-7-desoxy-9-epi-daunomycinone dimethylether (Example 3), there was obtained 4-demethoxy-7,9-bis-epi-daunomycinone, m.p. 185°-187°; $[\alpha]_D^{20} - 167^\circ$, $c = 0.1$, dioxane.

EXAMPLE 8

α (-)-Daunosaminy-4-demethoxy-daunomycinone (4-demethoxydaunomycin) (X; $R_1=R_2=R_3=H$) and β (-)-daunosaminy-4-demethoxy-daunomycinone (β -4-demethoxy-daunomycin) (X'; $R_1=R_2=R_3=H$).

To 1 gm. of 4-demethoxydaunomycinone (Example 5) in 200 ml. of benzene, 3 gm. of 1,2,3,6-tetradeoxy-4-O-trifluoroacetyl-3-trifluoroacetamido-L-lyxo-hex-1-enopyranose* and 30 mg. of p-toluenesulfonic acid were added. The solution was refluxed for 8 hrs. in the dark.

Pyridine (0.1 ml.) was added and the solution evaporated in vacuo. The residue was taken up in chloroform, washed with water and 5% NaHCO_3 . The solvent was evaporated in vacuo, the residue dissolved in 350 ml. of methanol and left overnight at room temperature. After evaporation of the solvent the residue was chromatographed on 20 gm. of silica gel, eluting first with chloroform, then with chloroform:acetone - 19:1 to give 0.6 gm. of $\alpha(-)$ -daunosaminyl-4-demethoxy-daunomycinone N-trifluoroacetate (X; $\text{R}_1=\text{R}_2=\text{R}_3=\text{H}$; $\text{R}_4=\text{COCF}_3$; m.p. $155^\circ\text{--}158^\circ$; $[\alpha]_D^{20} + 200^\circ$, c = 0.1, dioxane) and 0.30 gm. of $\beta(-)$ -daunosaminyl-4-demethoxy-daunomycinone N-trifluoroacetate (X'; $\text{R}_1=\text{R}_2=\text{R}_3=\text{H}$; $\text{R}_4=\text{COCF}_3$; m.p. $148^\circ\text{--}150^\circ\text{C}$; $[\alpha]_D^{20} + 100^\circ$, c = 0.1 dioxane). Compound X ($\text{R}_1=\text{R}_2=\text{R}_3=\text{H}$; $\text{R}_4=\text{COCF}_3$) was dissolved in 40 ml. of 0.1 N NaOH and kept at room temperature for 30 minutes. The solution was brought to pH 8 with HCl and extracted with chloroform. Evaporation of the solvent left a residue that was taken up in a little chloroform-methanol. Methanolic 0.1N HCl was added to adjust the pH to 4.5, after which sufficient ethyl ether was added to precipitate 0.35 gm. of the hydrochloride of $\alpha(-)$ -daunosaminyl-4-demethoxy-daunomycinone (4-demethoxy-daunomycin).

*Prepared in accordance with Example 2 of application, Ser. No. 568,437, filed Apr. 16, 1973, now abandoned.

(X; $\text{R}_1=\text{R}_2=\text{R}_3=\text{H}$; m.p. $183^\circ\text{--}185^\circ$; $[\alpha]_D^{20} + 210^\circ$, c = 0.1, CH_3OH). From Compound X' ($\text{R}_1=\text{R}_2=\text{R}_3=\text{H}$; $\text{R}_4=\text{COCF}_3$) and operating in an analogous manner, the hydrochloride of $\beta(-)$ -daunosaminyl-4-demethoxy-daunomycinone (β -4-demethoxy-daunomycin) (XI'; $\text{R}_1=\text{R}_2=\text{R}_3=\text{H}$; $[\alpha]_D^{20} + 124^\circ$, c = 0.1 $\text{C}_2\text{H}_5\text{OH}$) was obtained.

EXAMPLE 9

$\alpha(-)$ -Daunosaminyl-4-demethoxy-daunomycinone (4-demethoxydaunomycin) (X; $\text{R}_1=\text{R}_2=\text{R}_3=\text{R}_4=\text{H}$).

To a solution of 1 gm. of 4-demethoxy-daunomycinone (Example 5) in 230 ml. of anhydrous chloroform, 2.2 gm. of 2,3,6-trideoxy-3-trifluoroacetamido-4-O-trifluoroacetyl- α -L-lyxopyranosyl-chloride*, 2 gm. of HgO , 0.5 gm. of HgBr_2 and 15 gm. of 5A molecular sieve were added under stirring. The suspension was stirred in the dark for 24 hours, filtered, concentrated in vacuo and the residue dissolved in 350 ml. of methanol. The solution was left overnight at room temperature. After evaporation of the solvent the residue was chromatographed on 20 gm. of silica gel, eluting first with chloroform, then with chloroform:acetone 19:1 to give 0.55 gm. of $\alpha(-)$ -daunosaminyl-4-demethoxy-daunomycinone N-trifluoroacetate (X; $\text{R}_1=\text{R}_2=\text{R}_3=\text{H}$; $\text{R}_4=\text{COCF}_3$), which is then worked up as in Example 8, to give $\alpha(-)$ -daunosaminyl-4-demethoxy-daunomycinone hydrochloride. (X; $\text{R}_1=\text{R}_2=\text{R}_3=\text{R}_4=\text{H}$).

*Prepared in accordance with Example 2 of copending application, Ser. No. 560,103, filed Mar. 19, 1973, now U.S. Pat. No. 4,039,663.

EXAMPLE 10

$\alpha(-)$ -Daunosaminyl-4-demethoxy-7,9-bis-epi-daunomycinone
(α -7,9-bis-epi-4-demethoxy-daunomycin) (XI;
 $\text{R}_1=\text{R}_2=\text{R}_3=\text{R}_4=\text{H}$) and
 $\beta(-)$ -daunosaminyl-4-demethoxy-7,9-bis-epi-daunomycinone
(β -7,9-bis-epi-4-demethoxy-daunomycin) (XI';
 $\text{R}_1=\text{R}_2=\text{R}_3=\text{R}_4=\text{H}$).

Condensation of 4-demethoxy-7,9-bis-epi-daunomycinone (Example 7) with 1,2,3,6-tetra-deoxy-4-O-trifluoroacetyl-3-trifluoroacetamido-L-lyxo-hex-1-enopyranose as described in Example 8, produced α -7,9-bis-epi-4-demethoxy-daunomycin N-trifluoroacetate (XI; $\text{R}_1=\text{R}_2=\text{R}_3=\text{H}$; $\text{R}_4=\text{COCF}_3$; m.p. $210^\circ\text{--}215^\circ$; $[\alpha]_D^{20} - 91^\circ$, c = 0.1, dioxane) together with β -7,9-bis-epi-4-demethoxy-daunomycin N-trifluoroacetate (XI'; $\text{R}_1=\text{R}_2=\text{R}_3=\text{H}$; $\text{R}_4=\text{COCF}_3$; m.p. $165^\circ\text{--}167^\circ$; $[\alpha]_D^{20} - 270^\circ$, c = 0.1, dioxane). These compounds were separated by chromatography on silica gel column using chloroform: acetone (80:20 by volume) as the eluent. The subsequent hydrolysis of said compounds with 0.1 N NaOH as reported in Example 8, produced respectively α -7,9-bis-epi-4-demethoxy-daunomycin hydrochloride (XI; $\text{R}_1=\text{R}_2=\text{R}_3=\text{R}_4=\text{H}$; m.p. $205^\circ\text{--}207^\circ$; $[\alpha]_D^{20} - 80^\circ$, c = 0.1, CH_3OH) and β -7,9-bis-epi-4-demethoxy-daunomycin hydrochloride (XI'; $\text{R}_1=\text{R}_2=\text{R}_3=\text{R}_4=\text{H}$; m.p. $185^\circ\text{--}187^\circ$; $[\alpha]_D^{20} - 250^\circ$, c = 0.1, CH_3OH).

EXAMPLE 11

Daunomycinone (VIII'; $\text{R}_1=\text{R}_2=\text{H}$; $\text{R}_3=\text{OCH}_3$).

Condensation of 3-methoxyphthalic acid monomethyl ester monochloride with $(-)$ -1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin as described in Example 2 produced 7-desoxy-daunomycinone dimethyl ether (IV, configuration 9S; $\text{R}_1=\text{R}_2=\text{H}$; $\text{R}_3=\text{OCH}_3$; $[\alpha]_D^{20} - 37^\circ$, c = 1, CHCl_3) which was treated as described in Example 4 to give 7-(S)-methoxy-7-desoxy-daunomycinone dimethyl ether, which by treatment with AlCl_3 as described above, and in applicants' U.S. Pat. No. 3,963,760 which corresponds to British Pat. No. 1461190, yielded 7-(S)-methoxy-7-desoxy-daunomycinone. Treatment of this compound with trifluoroacetic acid as described in Example 5 produced daunomycinone (VIII'; $\text{R}_1=\text{R}_2=\text{H}$; $\text{R}_3=\text{OCH}_3$; m.p. $210^\circ\text{--}213^\circ$; $[\alpha]_D^{20} + 175^\circ$, c = 0.1, dioxane).

EXAMPLE 12

7,9-bis-epi-Daunomycinone (VIII''; $\text{R}_1=\text{R}_2=\text{H}$; $\text{R}_3=\text{OCH}_3$).

Operating as described in Example 11, but employing $(+)$ -1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin, there was obtained 7,9-bis-epi-daunomycinone (VIII''; $\text{R}_1=\text{R}_2=\text{H}$; $\text{R}_3=\text{OCH}_3$; m.p. $210^\circ\text{--}213^\circ$; $[\alpha]_D^{20} + 176^\circ$, c = 0.1 dioxane).

EXAMPLE 13

7,9-bis-epi-Daunomycin (XI; $\text{R}_1=\text{R}_2=\text{H}$; $\text{R}_3=\text{OCH}_3$; $\text{R}_4=\text{H}$).

Operating as described in Example 8, but employing 7,9-bis-epi-daunomycinone (Example 12), there was obtained 7,9-bis-epi-daunomycin (XI; $\text{R}_1=\text{R}_2=\text{H}$; $\text{R}_3=\text{OCH}_3$; $\text{R}_4=\text{H}$).

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EXAMPLE 14

1-Methoxydaunomycinone (VIII'; $R_1=H$;
 $R_2=R_3=OCH_3$).

Condensation of 3,6-dimethoxyphthalic acid mono-
methyl ester monochloride with (-)-1,4-dimethoxy-6-
hydroxy-6-acetyl-tetralin as described in Example 11,
gave 1-methoxydaunomycinone (VIII', $R_1=H$;
 $R_2=R_3=OCH_3$).

EXAMPLE 15

1-Methoxydaunomycin (X; $R_1=R_2=H$;
 $R_3=R_4=OCH_3$).

Operating as described in Example 8, but employing
1-methoxy-daunomycinone (Example 14), there was
obtained 1-methoxy-daunomycin (X; $R_1=R_2=H$;
 $R_3=R_4=OCH_3$).

EXAMPLE 16

1-Methoxy-7,9-bis-epi-daunomycinone (VIII"; $R_1=H$;
 $R_2=R_3=OCH_3$).

Operating as described in Example 14, but employing
(+)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin, there
was obtained 1-methoxy-7,9-bis-epi-daunomycinone
(VIII"; $R_1=H$; $R_2=R_3=OCH_3$).

EXAMPLE 17

1-Methoxy-7,9-bis-epi-daunomycin (XI; $R_1=R_2=H$;
 $R_3=R_4=OCH_3$).

Operating as described in Example 8, but employing
1-methoxy-7,9-bis-epi-daunomycinone (Example 16),
there was obtained 1-methoxy-7,9-bis-epi-daunomycin (XI;
 $R_1=R_2=H$; $R_3=R_4=OCH_3$).

EXAMPLE 18

4-Demethoxy-1,4-dimethyl-daunomycinone (VIII';
 $R_1=H$; $R_2=R_3=CH_3$).

Condensation of 3,6-dimethylphthalic acid mono-
methyl ester monochloride with (-)-1,4-dimethoxy-6-
hydroxy-6-acetyl-tetralin as described in Examples 2, 4
and 5, yielded 4-demethoxy-1,4-dimethyl-daunomyci-
none (VIII', $R_1=H$; $R_2=R_3=CH_3$).

EXAMPLE 19

4-Demethoxy-1,4-dimethyl-7,9-bis-epi-daunomycinone
(VIII"; $R_1=H$; $R_2=R_3=CH_3$).

Operating as described in Example 18, but employing
(+)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin, there
was obtained 4-demethoxy-1,4-dimethyl-7,9-bis-epi-
daunomycinone (VIII"; $R_1=H$; $R_2=R_3=CH_3$).

EXAMPLE 20

4-Demethoxy-1,4-dimethyl-daunomycin (X;
 $R_1=R_2=H$; $R_3=R_4=CH_3$).

Operating as described in Example 8, but employing
4-demethoxy-1,4-dimethyl-daunomycinone (Example 18),
there was obtained 4-demethoxy-1,4-dimethyl-
daunomycin (X; $R_1=R_2=H$; $R_3=R_4=CH_3$).

EXAMPLE 21

4-Demethoxy-1,4-dimethyl-7,9-bis-epi-daunomycin
(XI; $R_1=R_2=H$; $R_3=R_4=CH_3$).

Operating as described in Example 20, but employing
4-demethoxy-1,4-dimethyl-7,9-bis-epi-daunomycinone
(Example 19), there was obtained 4-demethoxy-1,4-

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dimethyl-7,9-bis-epi-daunomycin (XI; $R_1=R_2=H$;
 $R_3=R_4=CH_3$).

EXAMPLE 22

4-Demethoxy-1,4-dichloro-daunomycinone (VIII';
 $R_1=H$; $R_2=R_3=Cl$).

Condensation of 3,6-dichlorophthalic acid mono-
methyl ester monochloride with (-)-1,4-dimethoxy-6-
hydroxy-6-acetyl-tetralin as described in Examples 2, 4
and 5, yielded 4-demethoxy-1,4-dichloro-daunomyci-
none (VIII'; $R_1=H$; $R_2=R_3=Cl$).

EXAMPLE 23

4-Demethoxy-1,4-dichloro-7,9-bis-epi-daunomycinone
(VIII"; $R_1=H$; $R_2=R_3=Cl$).

Operating as described in Example 22 but employing
(+)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin, there
was obtained 4-demethoxy-1,4-dichloro-7,9-bis-epi-
daunomycinone (VIII"; $R_1=H$; $R_2=R_3=Cl$).

EXAMPLE 24

4-Demethoxy-1,4-dichloro-daunomycin (X;
 $R_1=R_2=H$; $R_3=R_4=Cl$).

Operating as in Example 8, but employing 4-deme-
thoxy-1,4-dichloro-daunomycinone (Example 22), there
was obtained 4-demethoxy-1,4-dichloro-daunomycin
(X; $R_1=R_2=H$; $R_3=R_4=Cl$).

EXAMPLE 25

4-Demethoxy-1,4-dichloro-7,9-bis-epi-daunomycin (XI;
 $R_1=R_2=H$; $R_3=R_4=Cl$).

Operating as in Example 8, but employing 4-deme-
thoxy-1,4-dichloro-7,9-bis-epi-daunomycinone (Exam-
ple 23), there was obtained 4-demethoxy-1,4-dichloro-
7,9-bis-epi-daunomycin (XI; $R_1=R_2=H$; $R_3=R_4=Cl$).

EXAMPLE 26

4-Demethoxy-1,4-dibromo-daunomycinone (VIII';
 $R_1=H$; $R_2=R_3=Br$).

Condensation of 3,6-dibromophthalic acid monoethyl
ester monochloride with (-)-1,4-dimethoxy-6-
hydroxy-6-acetyl-tetralin as described in Examples 2, 4
and 5, yielded 4-demethoxy-1,4-dichloro-daunomyci-
none (VIII'; $R_1=H$; $R_2=R_3=Br$).

EXAMPLE 27

4-Demethoxy-1,4-dibromo-7,9-bis-epi-daunomycinone
(VIII"; $R_1=H$; $R_2=R_3=Br$).

Operating as described in Example 26, but employing
(+)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin, there
was obtained 4-demethoxy-1,4-dibromo-7,9-bis-epi-
daunomycinone (VIII"; $R_1=H$; $R_2=R_3=Br$).

EXAMPLE 28

4-Demethoxy-1,4-dibromo-daunomycin (X;
 $R_1=R_2=H$; $R_3=R_4=Br$).

Operating as in Example 8, but employing 4-deme-
thoxy-1,4-dibromo-daunomycinone (Example 26), there
was obtained 4-demethoxy-1,4-dibromo-daunomycin
(X; $R_1=R_2=H$; $R_3=R_4=Br$).

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EXAMPLE 29

4-Demethoxy-1,4-dibromo-7,9-bis-epi-daunomycin (XI; $R_1=R_2=H$; $R_3=R_4=Br$).

Operating as in Example 8, but employing 4-demethoxy-1,4-dibromo-7,9-bis-epi-daunomycinone (Example 27), there was obtained 4-demethoxy-1,4-dibromo-7,9-bis-epi-daunomycin (XI; $R_1=R_2=H$; $R_3=R_4=Br$).

EXAMPLE 30

4-Demethoxy-2,3-dimethyl-daunomycinone (VIII'; $R_1=CH_3$; $R_2=R_3=H$).

Condensation of 4,5-dimethylphthalic acid monomethyl ester monochloride with (-)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin as described in Example 2, yielded 4-demethoxy-2,3-dimethyl-daunomycinone dimethyl ether; m.p. 158°-160°, $[\alpha]_D^{20} - 40^\circ$ ($c = 0.1$, $CHCl_3$). By bromination and trifluoroacetic acid treatment as described in Examples 4 and 5, there were obtained, after chromatographic separation on silica gel, 4-demethoxy-2,3-dimethyl-daunomycinone, (VIII'; $R_1=CH_3$; $R_2=R_3=H$); m.p. 208°-210°, $[\alpha]_D^{20} + 160^\circ$, $c = 0.1$, $CHCl_3$; and 4-demethoxy-7-epi-2,3-dimethyl-daunomycinone (VIII'''; $R_1=CH_3$; $R_2=R_3=H$); $[\alpha]_D^{20} - 80^\circ$; $c = 0.1$, $CHCl_3$.

EXAMPLE 31

4-Demethoxy-2,3-dimethyl-7,9-bis-epi-daunomycinone (VIII''; $R_1=CH_3$; $R_2=R_3=H$).

Operating as described in Example 30, but employing (+)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin, there was obtained 4-demethoxy-2,3-dimethyl-7,9-bis-epi-daunomycinone (VIII''; $R_1=CH_3$; $R_2=R_3=H$; m.p. 209°-210°; $[\alpha]_D^{20} - 162^\circ$, $c = 0.1$, $CHCl_3$).

EXAMPLE 32

4-Demethoxy-2,3-dimethyl-daunomycin (X; $R_1=CH_3$; $R_2=R_3=H$).

Operating as described in Example 8, but employing 4-demethoxy-2,3-dimethyl-daunomycinone (Example 30), α -4-demethoxy-2,3-dimethyl-daunomycin N-trifluoroacetate was isolated (X; $R_1=CH_3$; $R_2=R_3=H$; $R_4=COCF_3$; m.p. 233°-235°; $[\alpha]_D^{20} + 181^\circ$, $c = 0.1$, dioxane) from which, by subsequent hydrolysis with 0.1 N NaOH, there was obtained α -4-demethoxy-2,3-dimethyl-daunomycin hydrochloride (X; $R_1=CH_3$; $R_2=R_3=H$; m.p. 190°-192°; $[\alpha]_D^{20} + 180^\circ$, $c = 0.1$, CH_3OH).

EXAMPLE 33

4-Demethoxy-2,3-dimethyl-7,9-bis-epi-daunomycin (XI; $R_1=CH_3$; $R_2=R_3=R_4=H$).

Operating as in Example 8, but employing 4-demethoxy-2,3-dimethyl-7,9-bis-epi-daunomycinone (Example 31), there was obtained 4-demethoxy-2,3-dimethyl-7,9-bis-epi-daunomycin hydrochloride (XI; $R_1=CH_3$; $R_2=R_3=R_4=H$).

EXAMPLE 34

4-Demethoxy-2,3-dimethoxy-daunomycinone (VIII'; $R_1=OCH_3$; $R_2=R_3=H$).

Condensation of 4,5-dimethoxyphthalic acid monomethyl ester monochloride with (-)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin as described in Example 11,

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gave 4-demethoxy-2,3-dimethoxy-daunomycinone (VIII'; $R_1=OCH_3$, $R_2=R_3=H$).

EXAMPLE 35

4-Demethoxy-2,3-dimethoxy-7,9-bis-epi-daunomycinone (VIII''; $R_1=OCH_3$; $R_2=R_3=H$).

Operating as in Example 34, but employing (+)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin, there was obtained 4-demethoxy-2,3-dimethoxy-7,9-bis-epi-daunomycinone (VIII''; $R_1=OCH_3$; $R_2=R_3=H$).

EXAMPLE 36

4-Demethoxy-2,3-dimethoxy-daunomycin (X; $R_1=OCH_3$; $R_2=R_3=R_4=H$).

Operating as in Example 8, but employing 4-demethoxy-2,3-dimethoxydaunomycinone (Example 34), there was obtained 4-demethoxy-2,3-dimethoxy-daunomycin hydrochloride (X; $R_1=OCH_3$; $R_2=R_3=R_4=H$).

EXAMPLE 37

4-Demethoxy-2,3-dimethoxy-7,9-bis-epi-daunomycin (XI; $R_1=OCH_3$; $R_2=R_3=R_4=H$).

Operating as in Example 8, but employing 4-demethoxy-2,3-dimethoxy-7,9-bis-epi-daunomycinone (Example 35), there was obtained 4-demethoxy-2,3-dimethoxy-7,9-bis-epi-daunomycin hydrochloride (XI; $R_1=OCH_3$; $R_2=R_3=R_4=H$).

EXAMPLE 38

4-Demethoxy-2,3-dichloro-daunomycinone (VIII'; $R_1=Cl$; $R_2=R_3=H$).

Condensation of 4,5-dichlorophthalic acid monomethyl ester monochloride with (-)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin as described in Example 2, gave 4-demethoxy-2,3-dichloro-daunomycinone dimethyl ether; m.p. 168°-170°, $[\alpha]_D^{20} - 28^\circ$ ($c = 1$, dioxane), which, by bromination and trifluoroacetic acid treatment as described in Examples 4 and 5, produced 4-demethoxy-2,3-dichlorodaunomycinone. (VIII'; $R_1=Cl$; $R_2=R_3=H$; m.p. 138°-140°).

EXAMPLE 39

4-Demethoxy-2,3-dichloro-7,9-bis-epi-daunomycinone (VIII''; $R_1=Cl$; $R_2=R_3=H$).

Operating as in Example 38, but employing (+)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin, there was obtained 4-demethoxy-2,3-dichloro-7,9-bis-epi-daunomycinone (VIII''; $R_1=Cl$; $R_2=R_3=H$; m.p. 137°-139°).

EXAMPLE 40

4-Demethoxy-2,3-dichloro-daunomycin (X; $R_1=Cl$; $R_2=R_3=R_4=H$).

Operating as in Example 8, but employing 4-demethoxy-2,3-dichloro-daunomycinone (Example 38) α -4-demethoxy-2,3-dichloro-daunomycin N-trifluoroacetate (X; $R_1=Cl$; $R_2=R_3=H$; $R_4=COCF_3$; m.p. 238°-240°; $[\alpha]_D^{20} + 170^\circ$, $c = 0.1$, dioxane) was isolated and from which by subsequent hydrolysis with 0.1 N NaOH, there was obtained α -4-demethoxy-2,3-dichloro-daunomycin hydrochloride (X; $R_1=Cl$; $R_2=R_3=R_4=H$; $[\alpha]_D^{20} + 180^\circ$, $c = 0.1$, CH_3OH).

EXAMPLE 41

4-Demethoxy-2,3-dichloro-7,9-bis-epi-daunomycin (XI; $R_1=Cl$; $R_2=R_3=R_4=H$).

Operating as in Example 8, but employing 4-demethoxy-2,3-dichloro-7,9-bis-epi-daunomycinone (Example 39), there was obtained 4-demethoxy-2,3-dichloro-7,9-bis-epi-daunomycin hydrochloride (XI; $R_1=Cl$; $R_2=R_3=R_4=H$).

EXAMPLE 42

4-Demethoxy-2,3-dibromo-daunomycinone (VIII'; $R_1=Br$; $R_2=R_3=H$).

Condensation of 4,5-dibromophthalic acid monomethyl ester monochloride with (-)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin as described in Examples 2, 4 and 5, gave 4-demethoxy-2,3-dibromo-daunomycinone (VIII'; $R_1=Br$; $R_2=R_3=H$).

EXAMPLE 43

4-Demethoxy-2,3-dibromo-7,9-bis-epi-daunomycinone (VIII'; $R_1=Br$; $R_2=R_3=H$).

Operating as in Example 42, but employing (+)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin, there was obtained 4-demethoxy-2,3-dibromo-7,9-bis-epi-daunomycinone (VIII'; $R_1=Br$; $R_2=R_3=H$).

EXAMPLE 44

4-Demethoxy-2,3-dibromo-daunomycin (X; $R_1=Br$; $R_2=R_3=R_4=H$).

Operating as in Example 8, but employing 4-demethoxy-2,3-dibromo-daunomycinone (Example 42), there was obtained 4-demethoxy-2,3-dibromo-daunomycin hydrochloride (X; $R_1=Br$; $R_2=R_3=R_4=H$).

EXAMPLE 45

4-Demethoxy-2,3-dibromo-7,9-bis-epi-daunomycin (XI; $R_1=Br$; $R_2=R_3=R_4=H$).

Operating as in Example 8, but employing 4-demethoxy-2,3-dibromo-7,9-bis-epi-daunomycinone (Example 43), there was obtained 4-demethoxy-2,3-dibromo-7,9-bis-epi-daunomycin hydrochloride (XI; $R_1=Br$; $R_2=R_3=R_4=H$).

EXAMPLE 46

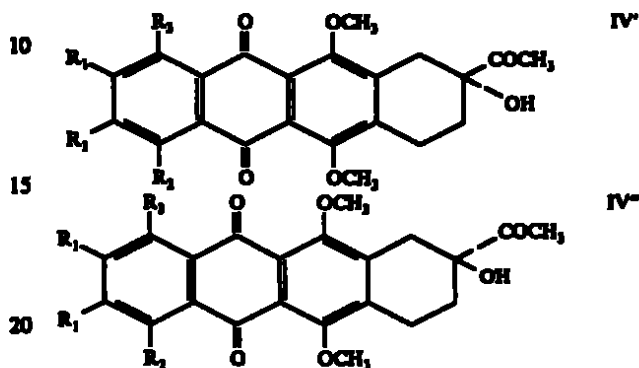
(+)-4-Demethoxy-7-desoxy-daunomycinone dimethyl ether (IV; $R_1=R_2=R_3=H$).

To 5 gm. of (+)-1,4-dimethoxy-6-hydroxy-6-acetyl-tetralin in 30 ml. of trifluoroacetic anhydride, 10 gm. of phthalic acid monomethyl ester were added and the solution refluxed for 18 hrs. The solution was evaporated in vacuo and the residue taken up in 100 ml. of 60% ethanol containing 8 gm. of NaOH. The solution was kept at 60° for 1 hr., diluted with water and extracted with chloroform which was then discarded. The aqueous solution was acidified with 2 N HCl and extracted with chloroform. Evaporation of the solvent left a residue that was dissolved in 20 ml. of liquid HF. After 3 hrs., the HF was evaporated and the residue taken up in chloroform. The chloroform extracts were washed with water and dilute NaOH and evaporated in vacuo. The residue was crystallized from ether to give 1.5 gm. of racemic 4-demethoxy-7-desoxy-daunomycinone dimethyl ether (IV; $R_1=R_2=R_3=H$; m.p. 184°-185°).

Variations and modifications can, of course, be made without departing from the spirit and scope of the invention.

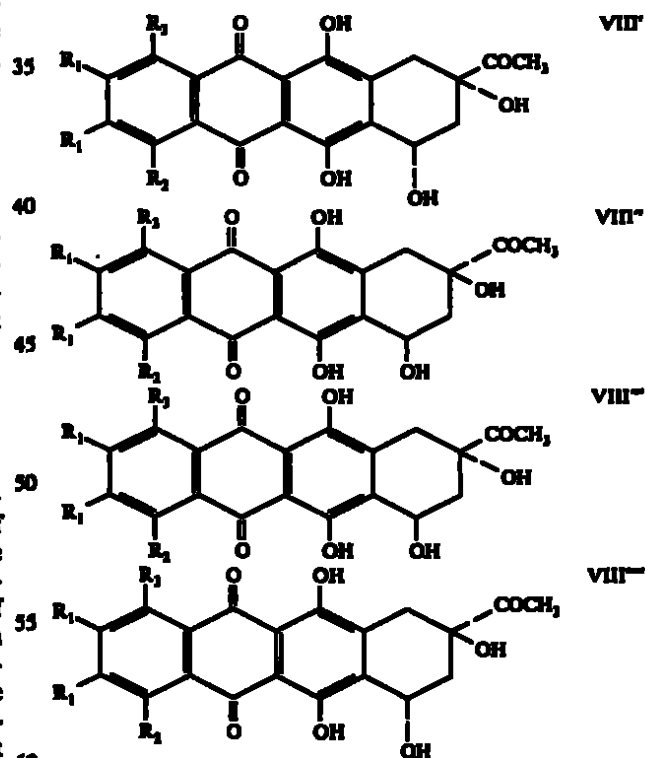
Having thus described our invention what we desire to secure by Letters Patent and hereby claim is:

1. Optically active anthracyclonones of the formulae IV' and IV''



wherein R₁ is hydrogen and R₂ and R₃ are the same and are hydrogen, methyl, methoxy, chlorine or bromine; or R₂ and R₃ are both hydrogen and R₁ is methyl, methoxy, chlorine or bromine; or R₁ and R₃ are both hydrogen and R₂ is methoxy with the proviso that R₁, R₂ and R₃ are not all simultaneously hydrogen in the case of formula IV'.

2. An optically active anthracyclonone of the general formula VIII', VIII'', VIII''' or VIII'''';



wherein R₁ is hydrogen and R₂ and R₃ are the same and are hydrogen, methyl, methoxy, chlorine or bromine; or R₂ and R₃ are both hydrogen and R₁ is methyl, methoxy, chlorine or bromine; or, in the case of formulae VIII'', VIII''' and VIII'''', R₁ and R₃ are both hydrogen and R₂ is methoxy.

UNITED STATES PATENT OFFICE Page 1 of 2
CERTIFICATE OF CORRECTION

Patent No. 4,077,988 Dated March 7, 1978

Inventor(s) Federico Arcamone et al

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 3, line 55: "diastereoisomeric" should read -- diastereoisomeric --; line 67: "keton" should read -- ketol --.

Column 4, line 29: "appropriatee" should read -- appropriate --.

Column 6, line 13: "ketoln" should read -- ketol --.

Column 12, line 20: " $R_1=R_2=R_3$ 50" should read -- $R_1=R_2=R_3=H$ --; line 58: " $[\alpha]_D^{20}$ 31 176°;" should read -- $[\alpha]_D^{20}$ -176°; --.

Column 14, line 12: " R_1H ;" should read -- $R_1=H$; --.

Column 15, line 23: " $R_2=R_3+H$);" should read -- $R_2=R_3=H$); --; line 40: " $R_2=R_3=H$)." should read -- $R_2=R_3=R_5=H$). --; line 50: " $[\alpha]_D^{20}$ " should read -- $[\alpha]_D^{20}$ --.

Column 16, lines 14-15: "4Demethoxy-2,3-dimethoxy-daunomycin (X; $R_1=OCH_3$ $R_2=R_3=R_5=H$)."

should read -- 4-Demethoxy-2,3-dimethoxy-daunomycin (X; $R_1=OCH_3$; $R_2=R_3=R_5=H$). --.

Column 17, line 19: " $R_2=R_3$ 50 H)." should read -- $R_2=R_3=H$). --.

UNITED STATES PATENT OFFICE Page 2 of 2
CERTIFICATE OF CORRECTION

Patent No. 4,077,988

Dated March 7, 1978

Inventor(s) Federico Arcamone et al

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 17, lines 48-49: "(+)-4-Demethoxy-7-desoxy-daunomycinone dimethyl ether (IV; R₁=R₂=R₃=H)." should read
-- (+)-4-Demethoxy-7-desoxy-daunomycinone dimethyl ether (IV; R₁=R₂=R₃=H). --.

Signed and Sealed this

Twenty-seventh Day of February 1979

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

DONALD W. BANNER
Commissioner of Patents and Trademarks

UNITED STATES PATENT OFFICE Page 1 of 2
CERTIFICATE OF CORRECTION

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 line 58: " $[\alpha]_D^{20}$ 31 176°;" should read -- $[\alpha]_D^{20}$ -176°; --.

Column 14, line 12: " R_1H ;" should read -- $R_1=H$; --.

Column 15, line 23: " $R_2=R_3+H$);" should read -- $R_2=R_3=H$); --;
 line 40: " $R_2=R_3=H$)." should read -- $R_2=R_3=R_5=H$). --; line 50:
 " $[\alpha]_D^0$ " should read -- $[\alpha]_D^{20}$ --.

Column 16, lines 14-15: "4Demethoxy-2,3-dimethoxy-daunomycin
 (X; $R_1=OCH_3$ $R_2=R_3=R_5=H$)." should read -- 4-Demethoxy-2,3-
 dimethoxy-daunomycin (X; $R_1=OCH_3$; $R_2=R_3=R_5=H$). --.

Column 17, line 19: " $R_2=R_3=50 H$)." should read -- $R_2=R_3=H$). --.

UNITED STATES PATENT OFFICE Page 2 of 2
CERTIFICATE OF CORRECTION

Patent No. 4,077,988 Dated March 7, 1978

Inventor(s) Federico Arcamone et al

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Column 17, lines 48-49: "(+)-4-Demethoxy-7-desoxy-daunomycinone dimethyl ether (IV; R₁=R₂=R₃=H)." should read
-- (+)-4-Demethoxy-7-desoxy-daunomycinone dimethyl ether (IV; R₁=R₂=R₃=H). --.

Signed and Sealed this

Twenty-seventh Day of February 1979

[SEAL]

Attest:

RUTH C. MASON
Attesting Officer

DONALD W. BANNER
Commissioner of Patents and Trademarks

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Gervasi, Gemma
NOTARBARTOLO & GERVASI S.P.A.
Corso di Porta Vittoria, 9
I-20122 Milano
ITALIE



PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing
(day/month/year) 09.01.2003

Applicant's or agent's file reference
2550PTWO/sbc

IMPORTANT NOTIFICATION

International application No.
PCT/EP01/13217

International filing date (day/month/year)
15/11/2001

Priority date (day/month/year)
16/11/2000

Applicant
MENARINI RICERCHE S.P.A. et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

For the purpose of deciding whether the claimed invention is patentable or not, the elected Offices may apply criteria additional to or different from the criteria on which the international preliminary examination report is based (see Articles 27(5), 33(5)). Additional criteria may include e.g. exemptions from patentability and the requirements of enabling disclosure and of clarity and support of claims.

Name and mailing address of the IPEA/

 European Patent Office - P.B. 6816 Patentlaan 2
NL-2280 HV Rijswijk - Pays Bas
Tel. +31 70 340 - 2040 Tlx 31 651 epo nl
Fax +31 70 340 - 3016

Authorized officer

Smith, K

Tel. +31 70 340-3479



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2550PTWO/sbc	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/EP01/13217	International filing date (day/month/year) 15/11/2001	Priority date (day/month/year) 16/11/2000
International Patent Classification (IPC) or national classification and IPC C07H15/252		
Applicant MENARINI RICERCHE S.P.A. et al		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 4 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand 10/06/2002	Date of completion of this report 09.01.2003
Name and mailing address of the international preliminary examining authority:  European Patent Office - P.B. 5816 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tlx 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Fitz, W Telephone No. +31 70 340 4359 

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP01/13217

I. Basis of the report

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, pages:

1-11 as originally filed

Claims, No.:

1-10 as received on 08/11/2002 with letter of 08/11/2002

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under Item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	1-10
	No:	Claims	-
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	-

2. Citations and explanations
see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: RHO, YOUNG S. ET AL: BULL. KOREAN CHEM. SOC. (2000), 21(8), 774-778, XP001058968

D2: RAO, A. V. RAMA ET AL: INDIAN J. CHEM., SECT. B (1985), 24B(7), 697-702, XP008000090

D1 is considered to be the closest prior art document. D1 describes the synthesis of a compound of formula I starting from a compound of formula II. D1 also describes that the compound of formula I is suitable for use as an intermediate for the synthesis of anthracycline antibiotics.

1.) The subject-matter of claims 1-10 is novel over D1 by virtue of the following differences:

The main difference between D1 and the present application is the following: in D1 the starting material i.e. the compound of formula II, is first formylated according to Vilsmeier-Haack. This is followed by Grignard addition of methyl magnesium bromide to the formyl-group obtained in the first step. In the application, on the other hand, the compounds of formula II are acylated with acetyl chloride in the presence of an excess of AlCl_3 at -35°C - 25°C , so that the desired C_2 -substituent is obtained in one step.

Another difference between D1 and the application is that in D1 an oxidation step of a hydroxyl group to a ketone group is required in order to finally arrive at the compound of formula I, whereas in the application no such oxidation is required.

2.) The subject-matter claims 1-10 involves an inventive step for the following reasons:

The problem to be solved by the application is considered to be the provision of a

further method for preparing tetralins of formula I starting from compounds of formula II, for use as intermediates towards anthracycline antibiotics.

The solution offered by the present application, i.e. a reaction sequence involving a Friedel Crafts acetylation of the compounds of formula II, is considered non-obvious in view of the available prior art documents. As a matter of fact, it is reported in the prior art (see D2, page 698, column 1) that this acetylation reaction has been unsuccessfully attempted, so that the authors were obliged to perform a Vilsmeier-Haack formylation instead.

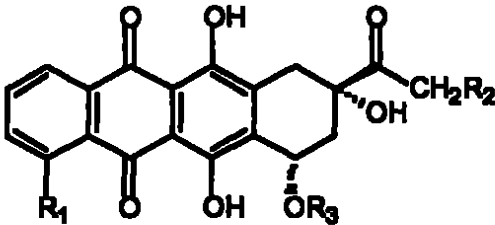
In conclusion, the subject-matter of claims 1-10 is considered to involve an inventive step.

Claims

12. 11. 2002

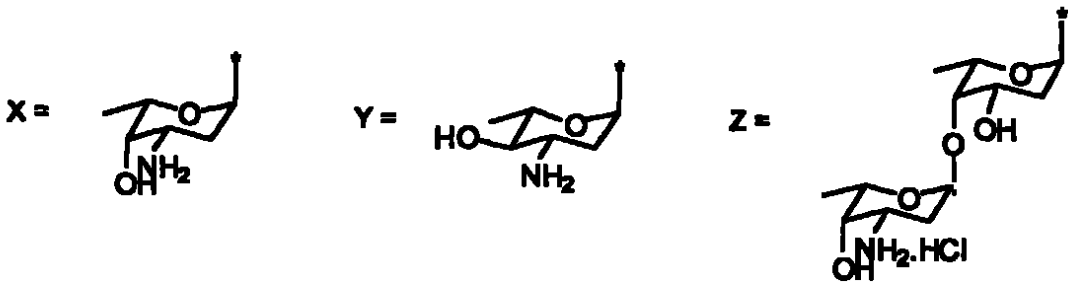
1. Process for the preparation of anthracycline of formula VIII:

(52)

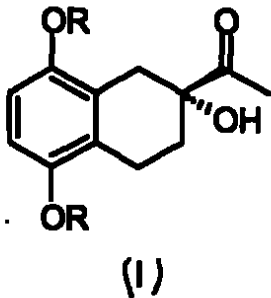


(VIII)

wherein $R_1 = H, OH, OCH_3$; $R_2 = H, OH$; $R_3 = X, Y$ or Z where:



comprising the formation of the intermediate of formula (I):

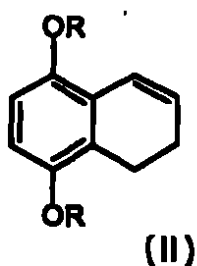


(I)

wherein: $R = C_{1-3}$, alkyl

characterised in that said intermediate of formula (I) is prepared starting from a 5-dialkoxy-3,4-dihydronaphthalene of formula (II):

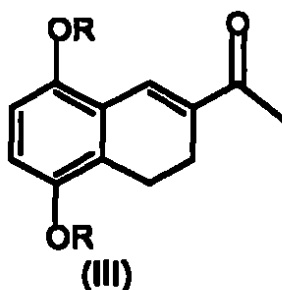
13



wherein R = C₁₋₃ alkyl

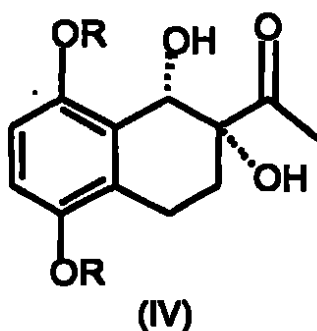
according to the following steps:

- 5 a) the 5,8-dialkoxy-3,4-dihydronaphthalene of formula (II), is acylated in a single step with acetyl chloride in the presence of an excess of AlCl₃ at a temperature comprised between -35° and 25° C, forming the corresponding acyl derivative (III)



wherein R = C₁₋₃ alkyl;

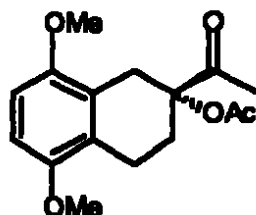
- 10 b) the acyl derivative (III) is enantioselectively hydroxylated with a catalytic quantity of osmium, to form the diol (IV)



wherein R = C₁₋₃ alkyl;

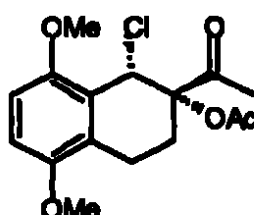
- 15 c) the diol (IV) is converted into the acetate (VI)

AMENDED SHEET



(VI)

by direct reduction or, alternatively, through the chloroacetate (V)



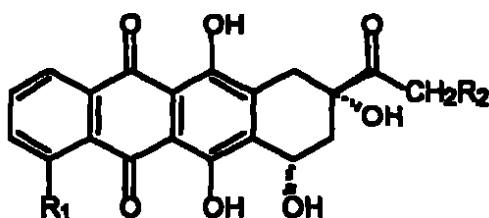
(V)

- 5 by reaction with triethylorthoacetate and trimethylsilylchloride followed by reduction according to known procedures;

d) the acetate (VI) is hydrolyzed to the tetralin of formula (I).

2. Process according to claim 1 wherein the tetralin of formula (I) is converted, according to known procedures, into the anthracyclinone of formula (VII),

10



VII

wherein $R_1 = H, OH, OCH_3$, $R_2 = H, OH, O\text{-acyl}$, wherein acyl is chosen between formyl, acetyl, mono- or di-chloroacetyl

- 15 and this is finally converted into the anthraccline of formula (VIII) as defined in Claim 1 according to known procedures.

3. Process according to claims 1 and 2 wherein $R = \text{methyl}$ and $R_2 = O\text{-acetyl}$.

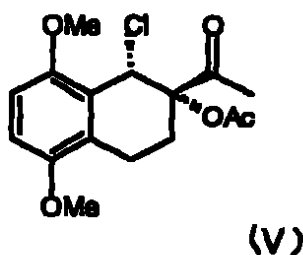
4. Process according to claim 1 wherein the acylation is performed at 0°C .

5. Process according to claim 1 wherein the enantioselective dihydroxylation
20 according to step (b) is performed using catalytic quantities of osmium using the

AMENDED SHEET

reactive AD-mix α with a further addition of an osmium salt and methanesulphonamide.

6. Process according to claim 5 wherein the osmium salt used is $K_2OsO_2(OH)_4$.
7. Process according to claim 6 wherein the reaction is performed at $-4 - +20^\circ C$.
- 5 8. Process according to claim 7 wherein the reaction is performed at $0^\circ C$.
9. Process according to claims 1 - 8 wherein the anthracyclines of formula (VIII) are: daunomicin (VIII, wherein $R_1 = OCH_3$, $R_2 = H$, $R_3 = X$), doxorubicin (VIII wherein: $R_1 = OCH_3$, $R_2 = OH$, $R_3 = X$), l'hydrarubicin (VIII wherein: $R_1 = H$, $R_2 = H$, $R_3 = X$) l'epirubicin (VIII, wherein: $R_1 = OCH_3$, $R_2 = OH$, $R_3 = Y$), or a tetracycline of
10 formula VIII wherein: $R_1 = H$, $R_2 = OH$, $R_3 = Z$, where X, Y and Z are as defined in claim 1.
10. Optically active compound of formula V



From the RECEIVING OFFICE

PCT

To:

Gervasi, Gemma
NOTARBARTOLO & GERVASI S.P.A.
Corso di Porta Vittoria, 9
I-20122 Milano
ITALIE

**NOTIFICATION OF THE INTERNATIONAL
APPLICATION NUMBER AND OF THE
INTERNATIONAL FILING DATE**

(PCT Rule 20.5(c))

Date of mailing
(day/month/year)

27 NOV 2001

Applicant's or agent's file reference
2550PTWO/sbc**IMPORTANT NOTIFICATION**International application No.
PCT/EP 01/ 13217International filing date (day/month/year)
15/11/2001Priority date (day/month/year)
16/11/2000Applicant
MENARINI RICERCHE S.P.A.

Title of the invention

1. The applicant is hereby notified that the international application has been accorded the international application number and the international filing date indicated above.
2. The applicant is further notified that the record copy of the international application was transmitted to the International Bureau on the above date of mailing.

3. ☐ Other: _____

* The International Bureau monitors the transmittal of the record copy by the receiving Office and will notify the applicant (with Form PCT/IB/301) of its receipt. Should the record copy not have been received by the expiration of 14 months from the priority date, the International Bureau will notify the applicant (Rule 22.1(c)).

Name and mailing address of the Receiving Office



European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040
Fax: (+31-70) 340-3016

Authorized officer

Mrs. H. Franz

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No. PCT/EP 01/13217

(15. 11. 2001) 15 NOV 2001
International Filing Date

EUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 2550PTWO/sbc

Box No. I TITLE OF INVENTION

Process for the synthesis of optically active anthracyclines

Box No. II APPLICANT

☐ This person is also inventor

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

MENARINI RICERCHE S.p.A.
Via Tito Speri 10
00040 POMEZIA (Province of ROME) - ITALY

Telephone No.

Facsimile No.

Teleprinter No.

Applicant's registration No. with the Office

State (that is, country) of nationality:

IT

State (that is, country) of residence:

IT

This person is applicant
for the purposes of:

☐ all designated
States

☒ all designated States except
the United States of America

☐ the United States
of America only

☐ the States indicated in
the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)

DI BUGNO Cristina
MENARINI RICERCHE S.p.A.
Via Tito Speri 10
00040 POMEZIA (Province of ROME) - ITALY

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only (If this check-box
is marked, do not fill in below.)

Applicant's registration No. with the Office

State (that is, country) of nationality:

IT

State (that is, country) of residence:

IT

This person is applicant
for the purposes of:

☐ all designated
States

☐ all designated States except
the United States of America

☒ the United States
of America only

☐ the States indicated in
the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf
of the applicant(s) before the competent International Authorities as:

☒ agent

☐ common
representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

GERVASI Gemma
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Agent's registration No. with the Office

☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)*If none of the following sub-boxes is used, this sheet should not be included in the request.*

Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> D'ARATA Fabio MENARINI RICERCHE S.p.A. Via Tito Speri 10 00040 POMEZIA (Province of ROME) - ITALY		This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i>
Applicant's registration No. with the Office		
State (that is, country) of nationality: IT	State (that is, country) of residence: IT	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box		
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> RAMACCIOTTI Alessio MENARINI RICERCHE S.p.A. Via Tito Speri 10 00040 POMEZIA (Province of ROME) - ITALY		This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i>
Applicant's registration No. with the Office		
State (that is, country) of nationality:	State (that is, country) of residence:	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box		
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> CROTTI Paolo MENARINI RICERCHE S.p.A. Via Tito Speri 10 00040 POMEZIA (Province of ROME) - ITALY		This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i>
Applicant's registration No. with the Office		
State (that is, country) of nationality: IT	State (that is, country) of residence: IT	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box		
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> 		This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i>
Applicant's registration No. with the Office		
State (that is, country) of nationality:	State (that is, country) of residence:	
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box		
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.		

Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☒ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT
- ☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☒ **EP** European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☒ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|---|--|--|
| ☒ AE United Arab Emirates | ☒ GH Ghana | ☒ MX Mexico |
| ☒ AG Antigua and Barbuda | ☒ GM Gambia | ☒ MZ Mozambique |
| ☒ AL Albania | ☒ HR Croatia | ☒ NO Norway |
| ☒ AM Armenia | ☒ HU Hungary | ☒ NZ New Zealand |
| ☒ AT Austria | ☒ ID Indonesia | ☒ PL Poland |
| ☒ AU Australia | ☒ IL Israel | ☒ PT Portugal |
| ☒ AZ Azerbaijan | ☒ IN India | ☒ RO Romania |
| ☒ BA Bosnia and Herzegovina | ☒ IS Iceland | ☒ RU Russian Federation |
| ☒ BB Barbados | ☒ JP Japan | |
| ☒ BG Bulgaria | ☒ KE Kenya | ☒ SD Sudan |
| ☒ BR Brazil | ☒ KG Kyrgyzstan | ☒ SE Sweden |
| ☒ BY Belarus | ☒ KP Democratic People's Republic of Korea | ☒ SG Singapore |
| ☒ BZ Belize | ☒ KR Republic of Korea | ☒ SI Slovenia |
| ☒ CA Canada | ☒ KZ Kazakhstan | ☒ SK Slovakia |
| ☒ CH & LI Switzerland and Liechtenstein | ☒ LC Saint Lucia | ☒ SL Sierra Leone |
| ☒ CN China | ☒ LK Sri Lanka | ☒ TJ Tajikistan |
| ☒ CO Colombia | ☒ LR Liberia | ☒ TM Turkmenistan |
| ☒ CR Costa Rica | ☒ LS Lesotho | ☒ TR Turkey |
| ☒ CU Cuba | ☒ LT Lithuania | ☒ TT Trinidad and Tobago |
| ☒ CZ Czech Republic | ☒ LU Luxembourg | ☒ TZ United Republic of Tanzania |
| ☒ DE Germany | ☒ LV Latvia | ☒ UA Ukraine |
| ☒ DK Denmark | ☒ MA Morocco | ☒ UG Uganda |
| ☒ DM Dominica | ☒ MD Republic of Moldova | ☒ US United States of America |
| ☒ DZ Algeria | | |
| ☒ EC Ecuador | ☒ MG Madagascar | ☒ UZ Uzbekistan |
| ☒ EE Estonia | ☒ MK The former Yugoslav Republic of Macedonia | ☒ VN Viet Nam |
| ☒ ES Spain | ☒ MN Mongolia | ☒ YU Yugoslavia |
| ☒ FI Finland | ☒ MW Malawi | ☒ ZA South Africa |
| ☒ GB United Kingdom | | ☒ ZW Zimbabwe |
| ☒ GD Grenada | | |
| ☒ GE Georgia | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☒ PH Philippines ☐ ☐
- ☒ OMAN ☐ ☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

S

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
item (1) 16 Nov. 2000 (16-11-00)	FI2000A000237	IT		
item (2)				
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA /

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

Number of
declarations

- | | | |
|---|--|---|
| ☐ Box No. VIII (i) | Declaration as to the identity of the inventor | : |
| ☐ Box No. VIII (ii) | Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent | : |
| ☐ Box No. VIII (iii) | Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application | : |
| ☐ Box No. VIII (iv) | Declaration of inventorship (only for the purposes of the designation of the United States of America) | : |
| ☐ Box No. VIII (v) | Declaration as to non-prejudicial disclosures or exceptions to lack of novelty | : |

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Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) the following number of sheets in paper form:

request (including declaration sheets) : 5
 description (excluding sequence listing part) : 11 [10]
 claims : 4 [2]
 abstract : 1
 drawings : _____

Sub-total number of sheets : 24

sequence listing part of description (actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below) : _____

Total number of sheets : 24

(b) sequence listing part of description filed in computer readable form

(i) ☐ only (under Section 801(a)(i))(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained (additional copies to be indicated under item 9(ii), in right column): _____

This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item):

- | | | |
|---|---|---|
| 1. ☐ fee calculation sheet | : | |
| 2. ☐ original separate power of attorney | : | |
| 3. ☐ original general power of attorney | : | |
| 4. ☐ copy of general power of attorney; reference number, if any: _____ | : | |
| 5. ☐ statement explaining lack of signature | : | |
| 6. ☐ priority document(s) identified in Box No. VI as item(s): _____ | : | |
| 7. ☐ translation of international application into (language): _____ | : | |
| 8. ☐ separate indications concerning deposited microorganism or other biological material | : | |
| 9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other)) | : | |
| (i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) | : | |
| (ii) ☐ (only where check-box (b)(i) or (b)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter | : | |
| (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column | : | |
| 10. ☒ other (specify): accompanying letter | : | 1 |

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: ENGLISH

Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).


 GERVASI Gamma

Milan, Nov. 14, 2001

For receiving Office use only

1. Date of actual receipt of the purported international application: (15. 11. 01) 15 NOV 2001	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☒ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

PATENT COOPERATION TREATY

57

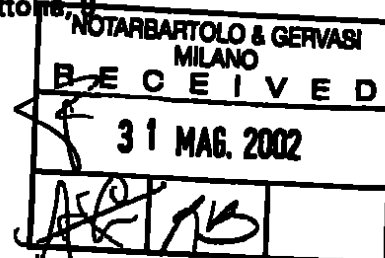
From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE
COMMUNICATION OF THE INTERNATIONAL
APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:

GERVASI, Gemma
Notarbartolo & Gervasi S.p.A.
Corso di Porta Vittoria, 8
I-20122 Milan
ITALIE

Date of mailing (day/month/year) 23 May 2002 (23.05.02)		
Applicant's or agent's file reference 2550PTWO/sbc		IMPORTANT NOTICE
International application No. PCT/EP01/13217	International filing date (day/month/year) 15 November 2001 (15.11.01)	Priority date (day/month/year) 16 November 2000 (16.11.00)
Applicant MENARINI RICERCHE S.P.A. et al		

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this notice:
KP, KR, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OA, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ,

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this notice is a copy of the international application as published by the International Bureau on 23 May 2002 (23.05.02) under No. WO 02/40496

4. TIME LIMITS for filing a demand for international preliminary examination and for entry into national phase

The applicable time limit for entering the national phase will, subject to what is said in the following paragraph be 30 MONTHS from the priority date, not only in respect of any elected Office if a demand for international preliminary examination is filed before the expiration of 18 months from the priority date, but also in respect of any designated Office, in the absence of filing of such demand, where Article 22(1) as modified with effect from 1 April 2002 applies in respect of the designated Office. For further details, see PCT Gazette No. 44/2001 of 1 November 2001, pages 19928, 19932 and 19934, as well as the PCT Newsletter, October and November 2001 and February 2002 issues.

In practice, time limits other than the 30-month time limit will continue to apply, for various periods of time, in respect of certain designated or elected Offices. For regular updates on the applicable time limits (20, 21, 30 or 31 months, or other time limit), Office by Office, refer to the PCT Gazette, the PCT Newsletter and the PCT Applicant's Guide, Volume II, National Chapters, all available from WIPO's Internet site, at <http://www.wipo.int/pct/en/index.html>.

For filing a demand for international preliminary examination, see the PCT Applicant's Guide, Volume I/A; Chapter IX. Only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination (at present, all PCT Contracting States are bound by Chapter II.)

It is the applicant's sole responsibility to monitor all these limits.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer J. Zahra Telephone No. (41-22) 338.91.11
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PATENT COOPERATION TREATY

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P. Achivion

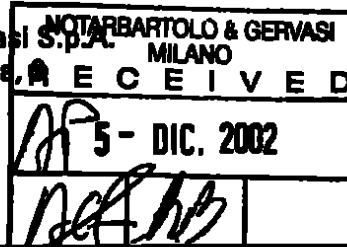
PCT

INFORMATION CONCERNING ELECTED
OFFICES NOTIFIED OF THEIR ELECTION

(PCT Rule 61.3)

From the INTERNATIONAL BUREAU

To:

GERVASI, Gemma
Notarbartolo & Gervasi S.p.A.
Corso di Porta Vittoria,
I-20122 Milan
Italy

Date of mailing (day/month/year) 19 November 2002 (19.11.02)		
Applicant's or agent's file reference 2550PTWO/sbc		IMPORTANT INFORMATION
International application No. PCT/EP01/13217	International filing date (day/month/year) 15 November 2001 (15.11.01)	Priority date (day/month/year) 16 November 2000 (16.11.00)
Applicant MENARINI RICERCHE S.P.A. et al		

1. The applicant is hereby informed that the International Bureau has, according to Article 31(7), notified each of the following Offices of its election:

EP : AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR
National : AU, BG, CA, CN, DE, GB, IL, JP, KP, KR, MN, NO, PL, RO, RU, SK, US

2. The following Offices have waived the requirement for the notification of their election; the notification will be sent to them by the International Bureau only upon their request:

AP : GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW
EA : AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
OA : BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
National : AE, AG, AL, AM, AT, AZ, BA, BB, BR, BY, BZ, CH, CO, CR, CU, CZ, DK, DM, DZ, EC, EE, ES, FI, GD, GE, GH, GM, HR, HU, ID, IN, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MW, MX, MZ, NZ, OM, PH, PT, SD, SE, SG, SI, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW

3. The applicant is reminded that he must enter the "national phase" before the expiration of 30 months from the priority date before each of the Offices listed above. This must be done by paying the national fee(s) and furnishing, if prescribed, a translation of the International application (Article 39(1)(a)), as well as, where applicable, by furnishing a translation of any annexes of the International preliminary examination report (Article 38(3)(b) and Rule 74.1).

Some offices have fixed time limits expiring later than the above-mentioned time limit. For detailed information about the applicable time limits and the acts to be performed upon entry into the national phase before a particular Office, see Volume II of the PCT Applicant's Guide.

The entry into the European regional phase is postponed until 31 months from the priority date for all States designated for the purposes of obtaining a European patent.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740.14.35	Authorized officer: Zakaria EL KHODARY Telephone No. (41-22) 338.83.38
--	--

**PCT
PETITORIO**

El abajo firmante solicita que la presente solicitud internacional sea procesada de acuerdo al Tratado de Cooperación en Materia de Patentes

No. de Solicitud Internacional
PCT/EP 01/13217
Fecha de presentación internacional
15-noviembre-2001
Nombre de la oficina receptora y "Solicitud Internacional de PCT Oficina de Patentes Europea - Solicitud Internacional PCT"
Referencia de archivo del solicitante o apoderado (si se desea) (12 caracteres máximo)
2550 PTWO/sbc

Bloque No. I TITULO DE LA INVENCION

Proceso para la síntesis de antraciclinas ópticamente activas

Bloque No. II SOLICITANTE

Nombre y dirección: (Apellido, seguido por nombre propio; para una entidad legal, designación oficial completa. La dirección debe incluir código postal y nombre del país.)	☐ Esta persona es también inventor
MENARINI RICERCHE S.p.A.	No. de teléfono:
Via Tito Speri 10	No. de facsimile:
00040 POMEZIA (Provincia de Roma) - ITALIA	No. de teleimpresora:

Estado (esto es, país) de nacionalidad:	Estado (esto es, país) de residencia:
IT	IT

Esta persona es solicitante ☐ todos los países designados ☒ todos los países designados excepto los Estados Unidos de Norteamérica ☐ los Estados Unidos de Norteamérica solamente ☐ los países indicados en el bloque complementario

Bloque No. III SOLICITANTES ADICIONALES Y/O INVENTORES (ADICIONALES)

Nombre y dirección: (Apellido, seguido por nombre propio; para una entidad legal, designación oficial completa. La dirección debe incluir código postal y nombre del país.)	Esta persona es:
DI BUGNO Cristina	☐ solicitante solamente
MENARINI RICERCHE S.p.A.	☒ solicitante e inventor
Via Tito Speri 10	☐ inventor solamente (si se marca este bloque, no llenar lo que sigue)
00040 POMEZIA (Provincia de Roma) - ITALIA	

Estado (esto es, país) de nacionalidad :	Estado (esto es, país) de residencia:
IT	IT

Esta persona es solicitante ☐ todos los países designados ☐ Todos los países designados excepto los Estados Unidos de Norteamérica ☒ los Estados Unidos de Norteamérica solamente ☐ los países indicados en el bloque complementario

☒ Solicitantes adicionales y/o inventores (adicionales) se indican en una hoja de continuación.

Bloque No. IV APODERADO O REPRESENTANTE COMUN; O DIRECCION PARA CORRESPONDENCIA

La persona identificada posteriormente es/ha sido citada para actuar en nombre del(los) solicitante(s) ante las Autoridades Internacionales competentes como: ☒ apoderado ☐ representante común

Nombre y dirección: (Apellido, seguido por nombre propio; para una entidad legal, designación oficial completa. La dirección debe incluir código postal y nombre del país.)	No. de teléfono:
GERVASI Gemma	+39 02541799.1
NOTARBARTOLO & GERVASI S.p.A.	No. de facsimile:
Corso di Porta Vittoria 9	+39 0254179920
20122 MILAN - ITALIA	No. de teleimpresora:

☐ Marque este bloque cuando ningún apoderado o representante común es/ha sido citado y el espacio anterior se usa en su lugar para indicar una dirección especial a la cual se debe enviar la correspondencia.

Bloque No. III SOLICITANTES ADICIONALES Y/O INVENTORES (ADICIONALES)

Nombre y dirección: <i>(Apellido, seguido por nombre propio; para una entidad legal, designación oficial completa. La dirección debe incluir código postal y nombre del país.)</i> D'ARATA Fabio MENARINI RICERCHE S.p.A. Via Tito Speri 10 00040 POMEZIA (Provincia de Roma) – ITALIA		Esta persona es: ☐ solicitante solamente ☒ solicitante e inventor ☐ inventor solamente (si se marca este bloque, no llenar lo que sigue)
Estado (esto es, país) de nacionalidad: IT	Estado (esto es, país) de residencia: IT	
Esta persona es solicitante para los propósitos de ☐ todos los países designados ☐ todos los países designados excepto los Estados Unidos de Norteamérica ☒ los Estados Unidos de Norteamérica solamente ☐ los países indicados en el bloque complementario		
Nombre y dirección: <i>(Apellido, seguido por nombre propio; para una entidad legal, designación oficial completa. La dirección debe incluir código postal y nombre del país.)</i> RAMACCIOTTI Alessio MENARINI RICERCHE S.p.A. Via Tito Speri 10 00040 POMEZIA (Provincia de Roma) – ITALIA		Esta persona es: ☐ solicitante solamente ☒ solicitante e inventor ☐ inventor solamente (si se marca este bloque, no llenar lo que sigue)
Estado (esto es, país) de nacionalidad:	Estado (esto es, país) de residencia:	
Esta persona es solicitante para los propósitos de ☐ todos los países designados ☐ todos los países designados excepto los Estados Unidos de Norteamérica ☒ los Estados Unidos de Norteamérica solamente ☐ los países indicados en el bloque complementario		
Nombre y dirección: <i>(Apellido, seguido por nombre propio; para una entidad legal, designación oficial completa. La dirección debe incluir código postal y nombre del país.)</i> CROTTI Paolo MENARINI RICERCHE S.p.A. Via Tito Speri 10 00040 POMEZIA (Provincia de Roma) – ITALIA		Esta persona es: ☐ solicitante solamente ☒ solicitante e inventor ☐ inventor solamente (si se marca este bloque, no llenar lo que sigue)
Estado (esto es, país) de nacionalidad: IT	Estado (esto es, país) de residencia: IT	
Esta persona es solicitante para los propósitos de ☐ todos los países designados ☐ todos los países designados excepto los Estados Unidos de Norteamérica ☒ los Estados Unidos de Norteamérica solamente ☐ los países indicados en el bloque complementario		
Nombre y dirección: <i>(Apellido, seguido por nombre propio; para una entidad legal, designación oficial completa. La dirección debe incluir código postal y nombre del país.)</i> 		Esta persona es: ☐ solicitante solamente ☐ solicitante e invento ☐ inventor solamente (si se marca este bloque, no llenar lo que sigue)
Estado (esto es, país) de nacionalidad:	Estado (esto es, país) de residencia:	
Esta persona es solicitante para los propósitos de ☐ todos los países designados ☐ todos los países designados excepto los Estados Unidos de Norteamérica ☐ los Estados Unidos de Norteamérica solamente ☐ los países indicados en el bloque complementario		
☒ Solicitantes adicionales y/o inventores (adicionales) se indican en una hoja de continuación.		

Bloque No. V DESIGNACION DE ESTADOS

Las siguientes designaciones se hacen mediante la presente bajo la regla 4.9(a) (marque los bloques aplicables; se debe marcar por lo menos uno):

Patente Regional

- ☒ AP Patente ARIPO: KE Kenia, MW Malawi, SD Sudan, SZ Swazilandia y cualquier otro país el cual sea contratante del Protocolo de Harare y del PCT.
- ☒ EA Patente Euroasiática: AZ Azerbaiyán, BY Bielorusia, KZ Kazajistán, RU Federación Rusa, TJ Tayikistán, TM Turkmenistán, y cualquier otro país el cual sea un Estado contratante de la Convención Euroasiática en Patentes y del PCT.
- ☒ EP Patente Europea: AT Austria, BE Bélgica, CH y LI Suiza y Liechtenstein, DE Alemania, DK Dinamarca, ES España, FR Francia, GB Reino Unido, GR Grecia, IE Irlanda, IT Italia, LU Luxemburgo, MC Mónaco, NL Países Bajos, PT Portugal, SE Suecia y cualquier otro país el cual sea un estado Contratante de la Convención de Patentes Europea y del PCT.
- ☒ OA Patente OAPI: BF Burkina Faso, BJ Benin, CF República CentroAfricana, CG Congo, CI Costa de Marfil, CM Camerún, GA Gabón, GN Guinea, ML Mali, MR Mauritania, NE Nigeria, SN Senegal, TD Chad, TG Togo y cualquier otro país el cual sea un estado miembro de la OAPI o estado Contratante PCT (si se desea otra clase de protección o tratamiento, especifique en la línea de puntos).

Patente Nacional (si se desea otra clase de protección o tratamiento, especifique en la línea de puntos):

- | | |
|---|--|
| ☒ AE Emiratos Árabes Unidos | ☒ LS Lesoto |
| ☒ AL Albania | ☒ LT Lituania |
| ☒ AM Armenia | ☒ LU Luxemburgo |
| ☒ AG Antigua y Barbuda | ☒ LV Letonia |
| ☒ AT Austria | ☒ MA Marruecos |
| ☒ AU Australia | ☒ MD República de Moldavia |
| ☒ AZ Azerbaiyán | ☒ MG Madagascar |
| ☒ BA Bosnia y Herzegovina | ☒ MK La antigua República Yugoslava de Macedonia |
| ☒ BB Barbados | ☒ MN Mongolia |
| ☒ BG Bulgaria | ☒ MW Malawi |
| ☒ BR Brasil | ☒ MX México |
| ☒ BY Bielorusia | ☒ MZ Mozambique |
| ☒ BZ Belice | ☒ NO Noruega |
| ☒ CA Canada | ☒ NZ Nueva Zelanda |
| ☒ CH y LI Suiza y Liechtenstein | ☒ PL Polonia |
| ☒ CN China | ☒ PT Portugal |
| ☒ CO Colombia | ☒ RO Rumania |
| ☒ CR Costa Rica | |
| ☒ CU Cuba | ☒ RU Federación Rusa |
| ☒ CZ República Checa | ☒ SD Sudán |
| ☒ DE Alemania | ☒ SE Suecia |
| ☒ DK Dinamarca | ☒ SG Singapur |
| ☒ DM Dominicana | ☒ SI Eslovenia |
| ☒ DZ Argelia | |
| ☒ EC Ecuador | ☒ SK Eslovaquia |
| ☒ EE Estonia | ☒ SL Sierra Leona |
| ☒ ES España | ☒ TJ Tayikistán |
| ☒ FI Finlandia | ☒ TM Turkmenistán |
| ☒ GB Reino Unido | ☒ TR Turquía |
| ☒ GD Granada | ☒ TT Trinidad y Tobago |
| ☒ GE Georgia | ☒ TZ República Unida de Tanzania |
| ☒ GH Ghana | ☒ UA Ucrania |
| ☒ GM Gambia | ☒ UG Uganda |
| ☒ HR Croacia | ☒ UB Estados Unidos de Norteamérica |
| ☒ HU Hungría | ☒ UZ Uzbekistán |
| ☒ ID Indonesia | ☒ VN Vietnam |
| ☒ IL Israel | ☒ YU Yugoslavia |
| ☒ IN India | ☒ ZA Sudáfrica |
| ☒ IS Islandia | ☒ ZW Zimbabue |
| ☒ JP Japón | |
| ☒ KE Kenia | |
| ☒ KG Kirgistan | |
| ☒ KP República Democrática Popular de Corea | |
| ☒ KR República de Corea | |
| ☒ KZ Kazajistán | |
| ☒ LC Santa Lucía | |
| ☒ LK Sri Lanka | |
| ☒ LR Liberia | |

Además de las designaciones hechas anteriormente, la solicitante también hace bajo la regla 4.9(b) todas las designaciones las cuales

Serán permitidas bajo el PCT, excepto las designaciones de:

El solicitante declara que aquellas designaciones adicionales están sujetas a confirmación y que cualquier designación la cual no sea confirmada antes de la expiración de los 15 meses a partir de la fecha de prioridad será considerada como abandono por el solicitante en la expiración de aquel límite de tiempo. (La confirmación de una designación consiste de la presentación de una notificación que especifique aquella designación y el pago de las cuotas de designación y confirmación. La confirmación debe llegar a la Oficina receptora dentro del límite de tiempo de 15 meses.)

Bloque No. VI REIVINDICACION DE PRIORIDAD Reivindicaciones de prioridad adicionales se indican en el bloque complementario. ☐			
La prioridad de la(s) siguiente(s) solicitud(es) anterior(es) se reivindica mediante la presente:			
Fecha de presentación (día, mes, año)	Número de solicitud	Solicitud Nacional País	Oficina de presentación (solo para solicitud regional o internacional)
Item (1) 16 de noviembre de 2000 (16.11.00)	F12000A000237	IT	
Item (2)			
Item (3)			
Marque el siguiente bloque si la copia certificada de la solicitud anterior va a ser expedida por la Oficina la cual para los propósitos de la presente solicitud internacional es la Oficina receptora (se puede requerir una cuota): ☐ La Oficina receptora es notificada mediante la presente que prepare y transmita a la Oficina Internacional una copia certificada de la(s) solicitud(es) anterior(es) identificada(s) anteriormente como item(s): (1); (2); (3)			
Bloque No. VII AUTORIDAD DE BUSQUEDA INTERNACIONAL			
Elección de la Autoridad de Búsqueda Internacional (ISA) (Si dos o más Autoridades de Búsqueda Internacional son competentes para llevar a cabo la búsqueda internacional, indique la Autoridad escogida; se puede utilizar el código de dos letras:) ISA/		Requirir el uso de resultados de una búsqueda anterior. Referencia a esa búsqueda (si una búsqueda anterior ha sido llevada a cabo o requisitada por la Autoridad de Búsqueda Internacional): País (u oficina regional): Fecha (día/mes/año): Número:	
Bloque No. VIII LISTA DE VERIFICACION; IDIOMA DE PRESENTACION			
La solicitud internacional contiene los siguientes Números de hojas: 1. petitorio 05 2. descripción 11 3. reivindicaciones 04 4. extracto 01 5. dibujos Total 21		Esta solicitud internacional items siguiente(s) item(s) marcado(s) está acompañada por el (los) a continuación: 1. ☐ hoja de cálculos de las cuotas 2. ☐ poder del apoderado firmado separado 3. ☐ copia del poder general del apoderado 4. ☐ copia del poder general del apoderado; número de referencia, si alguna..... 5. ☐ declaración que explique carencia de firma 6. ☐ documento(s) de prioridad identificados en el bloque No. VI como item(s): (1) 7. ☐ traducción de la solicitud internacional en (idioma): 8. ☐ indicaciones separadas concernientes a los micro-organismos depositados u otro material biológico.. 9. ☐ listado de secuencia de nucleótidos y/o aminoácidos (disco flexible) 10. ☒ otros (especificar). Carta anexa	
La figura No. de los dibujos debe adjuntarse al extracto		Idioma de la presentación De la Solicitud Internacional Inglés	
Bloque No. IX FIRMA DEL SOLICITANTE O APODERADO			
Enseguida de cada firma, indique el nombre de la persona que firma y la capacidad en la cual la persona firma (si tal capacidad no es obvia de la lectura del petitorio). GERVASI Gemma Milan, Nov. 14, 2001			

Para uso de la Oficina receptora solamente

1. Fecha del recibo real de la solicitud internacional alegada: 15-noviembre-2001	2. Dibujos ☐ recibidos: ☐ no recibidos:
3. Fecha corregida del vencimiento del recibo real a los documentos o dibujos recibidos posteriormente pero a tiempo que complementan la solicitud internacional alegada:	
4. Fecha del recibo a tiempo de las correcciones requeridas bajo el artículo 11(2) del PCT:	
5. Autoridad de Búsqueda Internacional especificada por la solicitante: ISA/	6. ☒ Transmisión de copia de búsqueda retardada hasta que la cuota de búsqueda sea pagada

Fecha del recibo de la copia de registro por la Oficina Internacional:

TRATADO DE COOPERACION EN MATERIA DE PATENTES

PCT

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

(Artículo 36 y Regla 70 del PCT)

Referencia de archivo del solicitante o apoderado : 2550PTWO/sbc	PARA UNA ACCION ADICIONAL	Véase la Notificación de transmisión del reporte de examen preliminar internacional (Forma PCT/PEA/416)
No. de solicitud internacional : PCT/EP01/13217	Fecha de presentación internacional (día/mes/año) : 15/11/2001	Fecha de prioridad (día/mes/año) : 16/11/2000
Clasificación de Patente Internacional (IPC) o clasificación nacional e IPC : C07H15/252		
Solicitante: MENARINI RICERCHE S.P.A. et al		

1. Este reporte de examen preliminar internacional ha sido preparado por esta Autoridad Examinadora Preliminar Internacional y se transmite al solicitante de acuerdo al Artículo 36.	
2. Este REPORTE consiste de un total de <u>5</u> hojas que incluyen esta portada.	
☒ Este reporte también está acompañado de ANEXOS, esto es, hojas de la descripción, reivindicaciones y/o dibujos los cuales han sido enmendados y son la base de este reporte y/u hojas que contienen rectificaciones hechas ante esta Autoridad. (véase Regla 70.16 y Sección 607 de las Instrucciones Administrativas bajo el PCT). Estos anexos consisten de un total de <u>4</u> Hojas.	
3. Este reporte contiene indicaciones que se relacionan con los siguientes ítems:	
I ☒ Base del reporte II ☐ Prioridad III ☐ No se establece opinión con respecto a novedad, paso o etapa inventiva y aplicabilidad industrial IV ☐ Carencia de unidad de la invención V ☒ Declaración justificada bajo el Artículo 35(2) con respecto a novedad, etapa inventiva o aplicabilidad industrial; citas y explicaciones que apoyan tal declaración. VI ☐ Ciertos documentos citados VII ☐ Ciertos defectos en la solicitud internacional VIII ☐ Ciertas observaciones en la solicitud internacional	
Fecha de presentación de la demanda : 10/06/2002	Fecha de consumación de este reporte : 09/01/2003
 Nombre y dirección de correspondencia de la ISA Oficina de Patentes Europea, P.B. 5818 Patentlaan 2 NL-2280 HV Rijewijk Tel. (+31-70) 340-2040, Tx 31 651 epo nl Fax: (+31-70) 340-3016	Funcionario Autorizado : Fitz, W Teléfono No. +31 70 340 4359

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No. PCT/EP01/13217

I Base del Reporte

1. Con respecto a los elementos de la Solicitud internacional (las hojas de sustitución las cuales han sido proporcionadas a la Oficina receptora en respuesta a una invitación bajo el artículo 14 son referidas en este reporte como "presentadas originalmente" y no se anexan al informe debido a que no contienen enmiendas (Reglas 70.16 y 70.17)).

Descripción, páginas:

1-11 como se presentaron originalmente

Reivindicaciones, No.:

1-10 como se recibieron el 08/11/2002 con la carta del 08/11/2002

2. Con respecto al idioma, todos los elementos marcados anteriormente fueron disponibles o proporcionados a esta Autoridad en el idioma en el cual se presentó la solicitud original, a menos de que se indique de otra manera bajo este inciso

Estos elementos fueron disponibles o proporcionados a esta Autoridad en el siguiente lenguaje, el cual es

- ☐ El idioma de una traducción proporcionada para los propósitos de la búsqueda internacional (bajo la Regla 23.1(b)).
- ☐ El idioma de la publicación de la solicitud internacional (bajo la Regla 48.3(b)).
- ☐ El idioma de una traducción proporcionada para los propósitos del examen preliminar internacional (bajo la regla 55.2 y/o 55.3).

3. Con respecto a cualquier nucleótido y/o secuencia aminoácida descrita en la solicitud internacional, el examen preliminar fue llevado a cabo en base a la secuencia listada:

- ☐ contenida en la solicitud internacional en forma escrita.
- ☐ presentada junto con la solicitud internacional disco flexible.
- ☐ proporcionada subsecuentemente a esta Autoridad en forma escrita.
- ☐ proporcionada subsecuentemente a esta Autoridad en disco flexible.
- ☐ la declaración de que la secuencia listada escrita proporcionada subsecuentemente no vá más allá de lo descrito en la solicitud internacional como se presentó ha sido proporcionada.

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No:

PCT/EP01/13217

- ☐ la declaración de que la información registrada en disco flexible es idéntica a la secuencia istada escrita ha sido proporcionada.

4. Las enmiendas han resultado en la cancelación de:

☐ la descripción, páginas:

☐ las reivindicaciones, Nos.:

☐ los dibujos, Hojas:

5. ☐ Este reporte ha sido establecido como si (alguna de) las enmiendas no hubieran sido efectuadas, ya que se considera que ellas van más allá de la descripción presentada originalmente (Regla 70.2 (c)) (Cualquier hoja reemplazada que contenga tales enmiendas debe ser referida al inciso 1 y anexada a este reporte.)

6. Observaciones adicionales, si es necesario.

V. Declaración justificada bajo el artículo 35(2) con respecto a la novedad, etapa inventiva o aplicabilidad industrial; citas y explicaciones que apoyan tal declaración.

1. Declaración

Novedad (N)	Si:	Reivindicaciones	1-10
	No:	Reivindicaciones	-
Etapa Inventiva (IS)	Si:	Reivindicaciones	1-10
	No:	Reivindicaciones	-
Aplicabilidad Industrial (IA)	Si:	Reivindicaciones	1-10
	No:	Reivindicaciones	-

2. Citas y explicaciones:
Ver hoja separada

REPORTE DE EXAMEN

Solicitud Internacional No. PCT/EP 01/13217

PRELIMINAR INTERNACIONAL-HOJA SEPARADA

REF. INCISO V

Declaración justificada bajo el Artículo 35(2) con respecto a la novedad, etapa inventiva o aplicabilidad industrial; citas y explicaciones que apoyan tal declaración

Se hace referencia a los siguientes documentos:

D1: RHO, YOUNG S. ET AL: BULL. KOREAN CHEM. SOC. (2000), 21(8), 774-778, XP001058968

D2: RAO, A.V. RAMA ET AL: INDIAN J. CHEM., SECT. B (1985), 24B(7), 697-702, XP008000090

Se considera que el D1 es el documento del arte previo más cercano. El D1 describe la síntesis de un compuesto de fórmula I a partir de un compuesto de fórmula II. D1 también describe que el compuesto de fórmula I es adecuado para usarse como un intermediario para la síntesis de antibióticos de antraciclina.

- 1.) La materia de las reivindicaciones 1 – 10 es novedosa con respecto a D1 en virtud de las siguientes diferencias:

La principal diferencia entre D1 y la presente solicitud es la siguiente: en D1 el material de partida i.e. el compuesto de fórmula II, es primeramente formulado de conformidad con Vilsmeier-Haack. Esto es seguido por la adición de Grignard de metil bromuro de magnesio al grupo formilo obtenido en la primera etapa. En la solicitud, por otro lado, los compuestos de fórmula II son acilados con cloruro de acetilo en la presencia de un exceso de $AlCl_3$ a $-35^{\circ}C - 25^{\circ}C$, tal que el sustituyente C2 deseado es obtenido en una etapa.

Otra diferencia entre D1 y la solicitud es que en D1 se requiere de una etapa de oxidación de un grupo hidroxilo a un grupo cetona con el fin de llegar finalmente al compuesto de fórmula I, mientras que en la solicitud no se requiere tal oxidación.

- 2.) La materia de las reivindicaciones 1-10 involucra una etapa inventiva por las siguientes razones:

El problema a ser resuelto por la solicitud se considera que es proporcionar un método adicional para preparar tetralinas de fórmula I a partir de compuestos de fórmula II, para usarse como intermediarios de los antibióticos de antraciclina.

REPORTE DE EXAMEN

Solicitud Internacional No. PCT/EP 01/13217

PRELIMINAR INTERNACIONAL-HOJA SEPARADA

La solución ofrecida por la presente solicitud, i.e. una secuencia de reacción que involucra una acetilación Friedel Crafts de los compuestos de fórmula II, se considera que no es obvia en vista de los documentos disponibles del arte previo. De hecho se reporta en el arte previo (ver D2, página 698, columna 1) que esta reacción de acetilación ha sido intentada sin éxito, tal que en lugar de esta, los autores estuvieron obligados a llevar a cabo una formilación Vilsmeier-Haack.

En conclusión, la materia de las reivindicaciones 1 a 10 es considerada como que involucra una etapa inventiva.

REPORTE DE BUSQUEDA INTERNACIONAL

No. de solicitud internacional

PCT/EP01/13217

A. CLASIFICACION DEL TEMA

IPC 7: C07H15/252 C07C69/14 //C07M7:00

De acuerdo a la Clasificación de Patentes Internacional (IPC) o a la clasificación nacional y a la IPC.

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación):

IPC7: C07H C07C

Documentación buscada diferente a la documentación mínima, a la extensión que tales documentos estén incluidos en los campos buscados:

Base de datos electrónicos consultados durante la búsqueda internacional (nombre de la base de datos y, en donde sea práctico, términos de búsqueda utilizados):

EPO-Internal, CHEM ABS Data

C. DOCUMENTOS QUE SE CONSIDERA QUE SON RELEVANTES

Categoría	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Relevante para la Reiv. No
X	RAO, A. V. RAMA ET AL: "A stereoconvergent synthesis of (+)-4-demethoxydaunomycin" J. CHEM. SOC., CHEM. COMMUN. (1984), (7), 453-5, XP002188353 * el documento completo, en particular la página 454, compuestos 2,3,6 y columna 2, último párrafo*	1, 9

X Documentos adicionales se enlistan en la continuación del bloque C X Véase familia de patentes anexa.

* Categorías especiales de los documentos citados

"A" documento que define el estado general de la técnica el cual no se considera ser de particular relevancia.

"E" documento anterior publicado en o después de la fecha de presentación internacional.

"L" documento el cual puede arrojar dudas sobre la(s) reivindicación(es) de prioridad o el cual se cita para establecer la fecha de publicación de otra cita u otra razón especial (como se especifica)

"O" documento que se refiere a una descripción oral, uso, exhibición u otro medio

"P" documento publicado antes de la fecha de presentación internacional pero después de la fecha de prioridad reivindicada.

"T" documento posterior publicado después de la fecha de presentación internacional o fecha de prioridad y no en conflicto con la solicitud, pero citado para entender el principio o teoría fundamental de la invención.

"X" documento de relevancia particular; la invención reivindicada no puede ser considerada nueva o no se puede considerar que involucre una etapa inventiva cuando el documento es considerado de manera aislada.

"Y" documento de particular relevancia; no se puede considerar que la invención involucre una etapa inventiva cuando el documento es combinado con uno o más de tales documentos, tal combinación sería obvia para una persona experimentada en la técnica.

"Z" documento miembro de la misma familia de patentes.

Fecha de la terminación real de la búsqueda internacional

29-enero -2002

Fecha de envío del reporte de búsqueda internacional

27/02/2002

Nombre y dirección de correspondencia de la ISA
Oficina de Patentes Europea, P.B. 5818 Patentlaan 2
NL-2280 HV Rijewijk
Tel. (+31-70) 340-2040, Tx 31 651 epo nl

Funcionario Autorizado

Fitz, W

REPORTE DE BUSQUEDA INTERNACIONAL

No. de solicitud internacional

PCT/EP 01/13217

C. (Continuación). DOCUMENTOS QUE SE CONSIDERA QUE SON RELEVANTES		
Categoría *	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Relevante para la Reiv. No.
X	RHO, YOUNG S. ET AL: "Total synthesis of a new 7-deoxyidarubicinone derivative through the functionalization of an A-ring side chain" BULL. KOREAN CHEM. SOC. (2000), 21(8), 774-778, XP001058968 * el documento completo, en particular pág. 774, compuestos 1 - 5 y esquema 1, compuestos 6 y 14; pág. 775, columna 2, Esquema 2; pág. 778, columna 1, ref. 4b*	1,9
X	DATABASE CA 'Online' CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TANNO NORIHIKO ET AL: "Preparation of dihydroxytetrahydronaphthacenedione derivatives as intermediates for anthracycline antibiotics" recuperado de STN Base de datos acceso no. 108:21533 XP002188593 *extracto, en particular CAS RN 112007-70-2* & JP 62 132838 A (SUMITOMO PHARMACEUTICALS CO., LTD., JAPAN) 16 de junio de 1987 (1987-06-16)	12
Y	NAKAJIMA, M. ET AL.: "Short-step asymmetric synthesis of anthracycline antibiotics via enantioselective dihydroxylation by osmium tetroxide with a chiral diamine" TETRAHEDRON vol. 49, no. 47, 1993, págs. 10807-10816, XP002188355 citado en la solicitud el documento completo	1-3, 6-12
Y	RAO, A. V. RAMA ET AL: "Total synthesis of (+,-)-4-demethoxydaunomycinone" INDIAN J. CHEM., SECT. B (1985), 24B(7), 697-702, XP008000090 * el documento completo, en particular la página 698, Esquema 1, compuestos 9 y 10; pág. 700, columna 1, último párrafo-columna 2, primer párrafo*	1-3, 6-12

REPORTE DE BUSQUEDA INTERNACIONAL

No. de solicitud internacional

PCT/EP 01/13217

C. (Continuación). DOCUMENTOS QUE SE CONSIDERA QUE SON RELEVANTES

Categoría *	Cita del documento, con indicación, en donde sea apropiado, de los pasajes relevantes	Relevante para la Reiv. No.
A	ARCAMONE, F. ET AL.: "Synthesis and antitumor activity of new adriamycin analogues" EXPERIENTIA, vol. 34, no. 10, 1978, págs. 1255-1257, XP002188354 el documento completo	1,11,12
A	US 4 077 988 A (ARCAMONE FEDERICO ET AL) 7 de marzo de 1978 (1978-03-07) * el documento completo, en particular columna 5, líneas 25-42*	1,11,12
A	RUSSELL, R.A. ET AL.: "An economical and Versatile synthesis of 5,8-dialcoxy-2-acetyl-3,4-dihydronaphthalen ex: key precursors for the synthesis of chiral anthracyclines" J. CHEM. SOC. CHEM. COMMUN., 1983, págs. 994-995, XP002188356 citada en la solicitud el documento completo	1,11,12

REPORTE DE BUSQUEDA INTERNACIONAL
Información en miembros de familia de patentes

No. de solicitud internacional
PCT/EP 01/13217

Documento de patente citado en el Reporte de Búsqueda	Fecha de publicación	Miembro(s) de la familia de patente(s)	Fecha de publicación

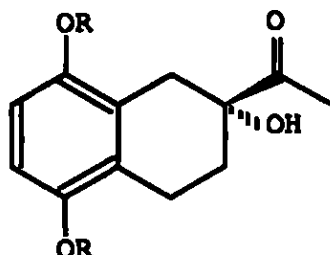
PCT		ORGANIZACION MUNDIAL DE LA PROPIEDAD INTELECTUAL Oficina Internacional		
SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACION EN MATERIA DE PATENTES (PCT)				
(51) Clasificación ⁷ internacional de patente:		A1	(11) Número de publicación internacional: WO 02/40496	
C07H 15/252 C07C 69/14//C07M 7:00			(43) Fecha de publicación internacional: 23 de mayo de 2002 (23.05.2002)	
(21) Número de solicitud internacional: PCT/EP01/13217		(74) Apoderado: GERVASEL, Gemma, Notarbartolo & Gervasi S.p.A., Corso di Porta Vittoria, 9, I-20122 Milan		
(22) Fecha de presentación internacional: 15 de noviembre de 2001 (15.11.2001)		(81) Países designados (nacional): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, GR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MY, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.		
(25) Idioma de Presentación: Inglés		(84) Países Designados (regional): Patente ARIPO (GH, OM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Patente euroasiática (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Patente europea (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), Patente OAPI (BF, BI, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).		
(26) Idioma de Publicación: Inglés		Publicada <i>Con reporte de búsqueda internacional</i>		
(30) Datos de prioridad: F12000A000237 16 de noviembre de 2000 (16.11.2000) IT		<i>Para códigos de dos letras y otras abreviaciones referirse a "Guías y Notas sobre Códigos y Abreviaciones" que aparece al principio de cada edición regular de la Gaceta del PCT</i>		
(71) Solicitante: (Para todos los países designados excepto para EUA): MENARINI RICERCHE S.p.A. [IT/IT]; Via Tito Speri, 10, I-00040 Pomezia (IT).				
(72) Inventores: e				
(75) Inventor/Solicitante: (solo para EUA): DI BUGNO, Cristina [IT/IT]; Menarini Ricerche S.p.A. Via Tito Speri, 10, I-00040 Pomezia (IT). D'ARATA, Fabio [IT/IT]; Menarini Ricerche S.p.A. Via Tito Speri, 10, I-00040 Pomezia (IT). RAMACCIOTTI, Alessio [-/IT]; Menarini Ricerche S.p.A. Via Tito Speri, 10, I-00040 Pomezia (IT). CROTTI, Paolo [IT/IT]; Menarini Ricerche S.p.A. Via Tito Speri, 10, I-00040 Pomezia (IT).				
(54) Título: PROCESO PARA LA SÍNTESIS DE ANTRACICLINAS ÓPTICAMENTE ACTIVAS.				
(57) Extracto: Se describe un proceso para la síntesis de antraciclina ópticamente activa caracterizado por el hecho de que el intermediario clave 5,8-dialoxi (R)-2-acetil-2-hidroxi-1,2,3,4-tetrahidronaftaleno se prepara a partir de 5,8-dialoxi-3,4-dihidronaftaleno mediante acilación, dihidroxilación asimétrica, transformación en cloroacetato, deshidrocloración e hidrólisis final.				

PROCESO PARA LA SÍNTESIS DE ANTRACICLINAS OPTICAMENTE ACTIVAS

Campo de la Invención

La presente invención se refiere a un proceso para la
 5 síntesis de antraciclinas ópticamente activas en donde el
 intermediario clave ópticamente activo 5, 8-dialcoxi (R)-2-
 acetil-2-hidroxi-1,2,3,4-tetrahidronaftaleno de fórmula I

10

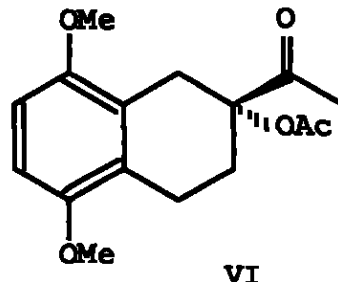
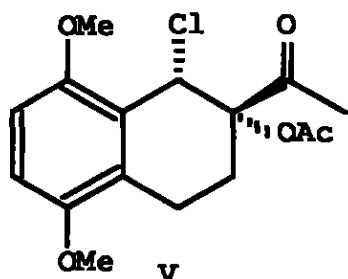


en donde: R es alquilo de 1 a 3 átomos de carbono,
 preferiblemente metilo;

se prepara a partir de 5,8-dialcoxi-3,4-dihidronaftaleno
 15 mediante acilación, dihidroxilación asimétrica,
 transformación en cloroacetato, deshidrocloración e
 hidrólisis final.

La presente invención también se refiere a los
 intermediarios de la fórmula V y VI:

20

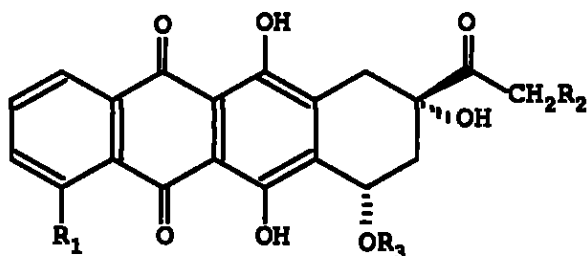


25 que tienen un exceso enantiomérico superior del 95%

Estado del Arte

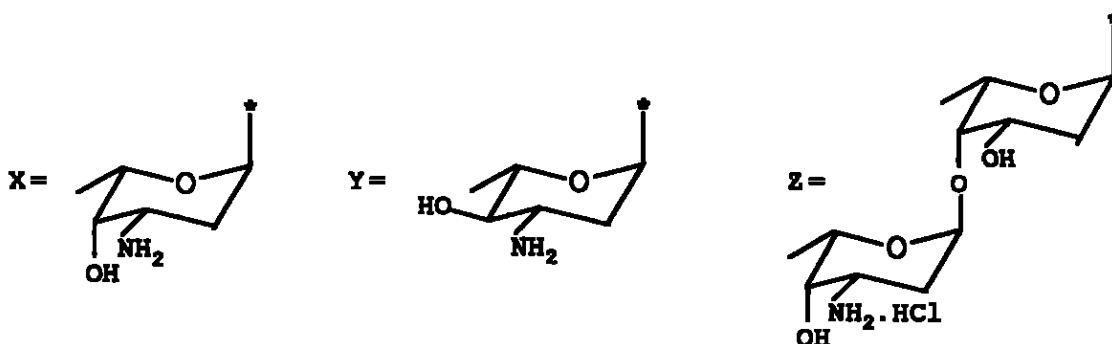
Como se sabe las antraciclinas de la fórmula VIII

5



en donde $R_1 = H, OH, OCH_3$; $R_2 = H, OH$; $R_3 = X, Y$ o Z donde

10



15 son compuestos que tienen un amplio uso terapéutico como fármacos anti-neoplásicos.

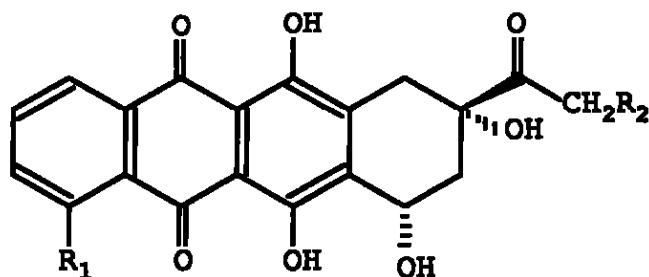
Los compuestos conocidos de fórmula VIII que tienen las propiedades antes dichas son por ejemplo Daunomicina (VIII en donde: $R_1 = OCH_3$, $R_2 = H$, $R_3 = X$), Doxorubicina (VIII en donde: $R_1 = OCH_3$, $R_2 = OH$, $R_3 = X$), Hidrarubicina (VIII en donde: $R_1 = H$, $R_2 = H$, $R_3 = X$), Epirubicina (VIII en donde: $R_1 = OCH_3$, $R_2 = OH$, $R_3 = Y$), o los compuestos descritos en la EP721456, en particular el compuesto de fórmula VIII en donde $R_1 = H$, $R_2 = OH$, $R_3 = Z$, la disacárido antraciclina que está ahora bajo
25 desarrollo clínico.

La síntesis de la antraciclina de fórmula VIII requiere de muchas etapas y se realiza normalmente a partir de una tetralina ópticamente activa de fórmula I que se hace reaccionar mediante una reacción Friedel Crafts con anhídrido ftálico o sus derivados como el ftaloil dicloruro o ftaloil cloruro metiléster y posteriormente ciclizada. El tetraciclo así obtenido está protegido en la posición 13-oxo con etilenglicol, está bromado en la posición 7 y es convertido en un derivado 7-OH con métodos conocidos (ver Arcamone et al., *Experientia*, 1978, 34, 1255; Wong et al. *Can. J. Chem.* 1971, 49, 2712,; Swenton et al., *Tetrahedron*, 1894, 40, 4625). Después de la desprotección la antraciclinona de la fórmula VII (en donde $R_2=H$) es usada como tal o es convertida en un derivado 14 aciloxi (compuesto de la fórmula VII en donde $R_2=O-acilo$) de conformidad con los procedimientos conocidos. Posteriormente los compuestos de fórmula VII son glicosidados con mono- o disacáridos protegidos como se describe en la literatura (ver Arcamona et al., *Experientia*, 1978, 34, 1255; Terashima et al., *Bull. Chem. Soc. Jpn.* 1986, 59, 423) y en EP....6, mediante desprotección se obtiene la antraciclina de fórmula VIII.

En los procesos antes descritos o en otros procesos similares que incluyen como intermediario una tetralina, el intermediario clave es en sí la tetralina de fórmula I como se definió anteriormente.

Esta síntesis AB synthon (Wong et al. Can. J. Chem. 1971, 49, 2712) permite la formación de la correspondiente antraciclinona ópticamente activa de fórmula VII en donde $R_1=H$, OH, OCH_3 y $R_2=H$, OH, O-acilo en donde el grupo acilo se
 5 selecciona de entre formilo, acetilo, mono-, di- o tricloroacetilo, preferiblemente acetilo.

10



Como se mencionó anteriormente el compuesto se convierte finalmente en la antraciclina deseada.

La estereoquímica de la posición C-9 de la
 15 antraciclinona es muy importante para la actividad biológica de estos compuestos ya que solo los compuestos que tienen configuración (S) en C-9 muestran una actividad antitumoral.

Posteriormente también el intermediario de tetralina de fórmula I debe obviamente tener la misma estereoquímica (i.e.
 20 una configuración absoluta R).

La tetralina I se prepara normalmente. De conformidad con la literatura, como una mezcla racémica partiendo de la 2-acetil-5,8-dimetoxi tetralina III por oxidación en la posición C-2 con t-butoxido de potasio/t-butanol en la
 25 presencia de oxígeno, seguida por la reducción "in-situ"

(Wong et al., Can. J. Chem. 1971, 49, 2712; Gardner et al., J. Org. Chem. 1968, 33, 3294).

El compuesto III se preparó con muy bajos rendimientos mediante la reacción del 5,8-dimetoxi-3,4-dihidronaftaleno II
5 con N,N-difenilacetamida- POCl₃ aplicando las condiciones de la reacción Vilsmeier-Haack seguida por la reducción del doble enlace.

Se han reportado varios intentos o ensayos para acilar los compuestos II pero todos sin éxito (Rama Rao et al. Ind.
10 J. Chem. 1985, 24B, 697).

Alternativamente los compuestos III se prepararon con un rendimiento de aproximadamente 50% en 4 pasos mediante la reacción del 5,8-diacetoxi-3,4-dihidronaftaleno con cloruro de acetilo/AlCl₃ y la formación de un derivado de
15 cloroacetilo, seguido por la deshidrocloración con LiCl, hidrólisis y metilación "in situ" (Russell et al. J. Chem. Soc. Chem. Comm. 1983, 994).

Otra trayectoria de reacción para obtener el precursor III reportado en la literatura incluye cinco pasos partiendo
20 del 5,8-dihidroxi-1,4-dihidronaftaleno con un rendimiento total de aproximadamente 50% (Giles et al. S. Afr. J. Chem. 1990, 43, 87).

La tetralina racémica I es convertida posteriormente en el compuesto enantiomérico puro usando los métodos normales
25 aplicados para la resolución de racemos a través de bases de

Schiff diastereoisoméricas sobre la cadena lateral de acetilo con (-)-1-feniletilamina (Arcamone et al. BP 02691/75, 1975). Alternativamente el compuesto enantiomérico puro se preparó por resolución cinética vía una epoxidación asimétrica
5 Sharpless seguida por la oxidación del alcohol de alilo obtenido mediante la reducción del 2-acetil-5,8-dimetoxi-3,4-dihidronaftaleno (Sharpless et al. J. Am. Chem. Soc. 1981, 103, 6237). Otro método para obtener la tetralina ópticamente pura consiste en la reducción estereoselectiva de la mezcla racémica con levadura de
10 panadería a mezclas de dioles diastereoisoméricas seguida por separación cromatográfica y re-oxidación (Terashima et al., Chem. Pharm. Bull. 1984, 32, 4328).

Una síntesis asimétrica de la tetralina I a partir del precursor III mediante dihidroxilación enantioselectiva está
15 descrita en M. Nakajima et al. Tetrahedron, 1993, 49, 10807, pero los varios pasos y el exceso final de la tetralina y especialmente el uso de tetraóxido de osmio en cantidades estequiométricas, en lugar de cantidades catalíticas y el uso de cantidades de aminas quirales costosas (siempre en
20 cantidades estequiométricas) a una temperatura de -110°C , hace muy difícil el uso industrial de esta síntesis.

Otras síntesis asimétricas de AB synthon que utilizan compuestos quirales o compuestos que comprenden derivados quirales de compuestos naturales están reportadas en la
25 literatura pero todas estas síntesis son muy complejas e

inadecuadas para aplicación industrial (Krohn, Angew. Chem. Int. Ed. Engl., 1986, 25, 790).

Sumario de la Invención

La presente invención describe un proceso para la
5 preparación de antraciclinas de fórmula VIII definida
anteriormente en donde la tetralina ópticamente activa de la
fórmula I antes definida se prepara estereoselectivamente a
partir del 5,8-dialcoxi-3,4-dihidronaftaleno II, el cual,
contrario a los métodos que aplican la resolución de mezclas
10 racémicas, que son difíciles de llevar a cabo y que dan
rendimientos inferiores al 30%, muestra la ventaja de
proporcionar el intermediario clave I en rendimientos mucho
mayores que aquellos reportados en la literatura y es fácil e
industrialmente explotable.

15 En particular, aunque la literatura reporta los intentos
por acilar los compuestos II como infructuosos o no
importantes debido a los bajos rendimientos, (Rama Rao et al.
Ind. J. Chem. 1985, 24B, 697, Russell et al. J. Chem. Soc.
Chem. Comm. 1983, 994, Giles et al. S. Afr. J. Chem. 1990,
20 43, 87), el 5,8-dialcoxi-3,4-dihidronaftaleno, (compuesto de
fórmula II en donde R es un grupo alquilo de 1 a 3 átomos de
carbono, preferiblemente metilo) puede sorprendentemente ser
acilado en solo una etapa en la presencia de un cloruro de
acilo y tricloruro de aluminio formando el correspondiente
25 derivado de acilo III. Además esta aplicación innovadora del

procedimiento de dihidroxilación catalítica enantioselectiva de olefinas (Sharpless et al., Chem. Rev. 1994, 94, 2483) para dar el derivado de acilo insaturado permite obtener el diol ópticamente activo de fórmula IV en un buen rendimiento. El compuesto es convertido
5 posteriormente en el correspondiente derivado de 1-cloro-2-acetilo mediante el procedimiento de Sharpless (Sharpless et al, Tetrahedron, 1992, 48, 10515) y deshalogenado siguiendo métodos conocidos, por ejemplo por hidrogenación catalítica o en la presencia de estaño y un precursor de radicales o puede ser directamente
10 deshidroxilado por reducción catalítica. La hidrólisis final del grupo éster permite la formación del compuesto I en buenos rendimientos y con una elevada pureza óptica.

DESCRIPCIÓN DETALLADA DE LA INVENCION

En el esquema I se ilustra un proceso para obtener la
15 tetralina de fórmula I en donde $R = CH_3$. En este caso el producto de partida es el 5,8-dimetoxi-3,4-dihidronaftaleno II, obtenido por métodos conocidos a partir de butadieno y p-quinona (Fieser et al., J. Am. Chem. Soc., 1948, 70, 3151).

A pesar del hecho de que en la literatura los intentos
20 por acilar el compuesto II fueron reportados como infructuosos o no importantes debido a los bajos rendimientos, el 5,8-dimetoxi-3,4-dihidronaftaleno II es tratado con cloruro de acetilo en la presencia de un exceso de tricloruro de aluminio, preferiblemente de 5 a 9 moles de
25 tricloruro de aluminio por una mol de cloruro de acilo, a una

temperatura de $-35^{\circ}\text{C} + 25^{\circ}\text{C}$, preferiblemente a 0°C . Después del tratamiento usual y cristalización con acetato de etilo, el producto, 2-acetil-5,8-dimetoxi-3,4-dihidronaftaleno se obtiene en rendimientos superiores al 70%.

5 El compuesto III es convertido estereoselectivamente a diol IV mediante una dihidroxilación asimétrica Sharpless la cual está descrita en la literatura para otros substratos de olefina (Sharpless et al., Chem. Rev. 1994, 94, 2483). El reactivo usado en esta etapa es la mezcla AD- α (catálogo
10 Aldrich, reactivo 39275-8, ver también J. Org. Chem. 1992, 57, 2768) con una adición complementaria de sal de sodio ($\text{K}_2\text{OsO}_2(\text{OH})_4$) y metansulfonamida.

La sal de osmio está siempre en una cantidad catalítica vis a vis el substrato. La reacción se lleva a cabo a una
15 temperatura baja, -4 a $+20^{\circ}\text{C}$, preferiblemente a 0°C , el rendimiento es de 70% con un exceso enantiomérico superior al 95%.

El diol IV ópticamente activo es convertido en un cloroacetato V a través de la formación "in situ" de un intermediario cíclico usando trimetilortoacetato en la presencia de un catalizador
20 ácido seguido por un tratamiento con trimetilsilil cloruro de conformidad con un método ya descrito en la literatura para diferentes dioles (Sharpless et al. Tetrahedron. 1992, 48, 10515). Esta etapa da rendimientos superiores al 80%.

La reducción del cloroacetato a acetato VI puede ser
25 llevado a cabo fotoquímicamente o mediante tratamiento

térmico en la presencia de tributilestanhidruro y precursores de radicales como el AIBN o BPO o por hidrogenación catalítica. Los rendimientos son superiores al 80%.

El acetato puede ser obtenido directamente mediante
5 reducción catalítica del diol IV.

La hidrólisis del acetato puede ser llevada a cabo con resinas de intercambio iónico en rendimientos cuantitativos. Alternativamente los métodos conocidos para la hidrólisis de los acetatos, como el tratamiento con metóxido de sodio o
10 hidróxido de sodio.

Lo ilustrado en el esquema I puede ser fácilmente aplicado para la síntesis de todos los compuestos de fórmula I usando los productos de partida correspondientes.

15 La tetralina I la cual es objeto de la presente invención es por lo tanto obtenida en solo 4 a 5 pasos con un rendimiento total mucho mayor que cualquiera reportado para los procesos conocidos.

Además, las condiciones de reacción como las
20 descritas hacen posible la extrapolación industrial del proceso. Los pasos subsecuentes del proceso a través de la antraciclinona a la antraciclina final se llevan a cabo de la manera descrita en la literatura.

El proceso de conformidad con la invención será mejor
25 entendido a la luz del Ejemplo reportado a continuación el

cual se refiere al esquema 1 i.e. a la preparación de la tetralina de fórmula I en donde $R = CH_3$.

Ejemplo 1

Síntesis de III

5 A una suspensión de tricloruro de aluminio (449 g) en diclorometano (2 l) en corriente de nitrógeno, se agregó cloruro de acetilo (380 ml) gota a gota a 0°C. Después de 30 minutos de agitación a 0°C, a la solución así obtenida se le agregó lentamente gota a
10 gota una solución de 5,8-dimetoxi-3,4-dihidronaftaleno II (80 g) en diclorometano (2.5 l). Después de 30 minutos bajo agitación a 0°C la mezcla se hidrolizó con hielo. Después de la separación de la fase orgánica y lavado con HCl 1N (3x6 l), H₂O (3x4 l)
15 y salmuera (2x4 l), el solvente se evaporó u.v. a 40°C dando un residuo sólido amarillo (98g). Por recristalización del acetato de etilo en reflujo se obtuvieron 71 g del compuesto deseado III.

Rendimiento del 73%.

20 ¹H RMN(CDCl₃): 2.44(s, 3H, H₁₀); 2.53(m, 2H, H₆); 2.80(m, 2H, H₅); 3.30, 3.84(2s, 6H, OCH₃); 6.75(dd, 2H, H₂+H₃); 7.81(m, 1H, H₈);

¹³C RMN (CDCl₃): 19.9, 20.5(C₅, C₆); 25.3(C₁₀); 55.9, 56.1(OCH₃); 108.5, 113.2(C₂, C₃); 122.6, 127.2(C_{4a}, C_{8a}); 131.5(C₈); 137.2(C₇); 150.4, 151.0(C₁, C₄); 198.8(C₉).

25 CCD: r.f. 0.80 (éter de petróleo/acetato de etilo = 80/20)

CLAR: r.t. = 8.9 min (condiciones: Lichrospher 100 RP 18 (5 μ m, 250x4mm) CH₃CN/H₂O + 0.1% TFA = 60/40; 1 ml/min; λ =214nm; 20 μ l de una solución 1 mg/10 ml).

Ejemplo 2

5 Síntesis de IV

A una solución de mezcla AD- α (600 g) y K₂OsO₂(OH)₄ (1g) en agua (2 l) se agregó t-butanol (2.15 l), metansulfonamida (40.7 g), y bicarbonato de sodio (109 g). La mezcla se agitó hasta la solución
10 completa de los componentes sólidos, se enfrió a 0°C, se agregó con 4-acetil-3,4-dihidronaftaleno (100 g) y se agitó vigorosamente por 96 h.

Después de completar la reacción del precursor, se checo por CCD (éter de petróleo/acetato de etilo =
15 80/20), se agregaron 630 g de bisulfito de sodio en porciones y, después de 1 hora de agitación, se agregaron 4 l de AcOEt y las fases se separaron.

La fase orgánica se lavó con NaOH 1 N (1 x 2 l), H₂O (1 x 2 l) y se evaporó bajo vacío.

20 El sólido obtenido se disolvió en 750 ml de CH₂Cl₂ y la solución se extrajo con H₂SO₄ al 3% saturado con K₂SO₄ (4 x 200 ml), NaHCO₃ s.s. (1 x 300 ml) y H₂O (1 x 300 ml)

La fase orgánica, seca en MgSO₄ anhidro, se evaporó bajo vacío dejando un residuo sólido.

El producto se cristalizó a partir de AcOEt/ciclohexano = 1/1, se filtró y se secó bajo vacío.

Se obtuvieron 78.7 g de un sólido cristalino. Rendimiento 70.5%.

5 ^1H RMN (CDCl_3): 1.87 (m, 2H, H_6); 2.38 (s, 3H, H_{10}); 2.79 (m, 2H, H_5); 3.78, 3.84 (2s, 6H, OCH_3); 3.81 (m, 1H, H_8); 4.87 (d, 1H, OH_8); 5.29 (s, 1H, OH_7); 6.71 (s, 2H, $\text{H}_2 + \text{H}_3$).

^{13}C RMN (CDCl_3): 19.1 (C_{10}); 25.8 (C_5); 28.7 (C_6); 55.7, 55.7 (OCH_3); 68.5 (C_8); 78.7 (C_7); 108.0, 108.8 (C_2, C_3); 125.8, 127.1 ($\text{C}_{4a}, \text{C}_{8a}$);
10 151.1, 152.3 (C_1, C_4); 214.2 (C_9).

CCD: r.f. 0.25 (éter de petróleo/acetato de etilo = 80/20)

CLAR: r.t. = 4.1 min (condiciones: Lichrospher 100 RP 18 (5 μm) 250x4 mm $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ + 0.1% TFA = 50/50; 1 ml/min; $\lambda=214\text{nm}$; 20 μl de una solución 2.8 mg/10 ml).

15 e.e.=98% determinada por CLAR quiral (condiciones: Quiralcel OD 250 x 4.6 mm; n-hexano/EtOH = 90/10; 1 ml/min; $\lambda=214\text{nm}$; 20 μl de una solución 1.3 mg/10 ml).

punto de fusión = 141-143°C.

$[\alpha]_D^{25} = -21.9^\circ$ (c=1.0, CHCl_3).

20 Ejemplo 3

Síntesis de V

A una solución de diol (77 g) en CH_2Cl_2 (600 ml), bajo nitrógeno, se agregaron trimetilortoacetato (59.3 ml) y piridinotoluen-4-sulfonato (2 g). La solución se agitó a

temperatura ambiente por 24 horas. El solvente se evaporó bajo vacío dejando un residuo sólido.

El sólido se solubilizó (CH_2Cl_2) (600 ml) y se agregó, bajo nitrógeno, con trimetilsilil cloruro (65 ml). La mezcla de reacción se agitó a temperatura ambiente por 1 hora y, después de la evaporación del solvente bajo vacío se trató con ciclohexano (400 ml) bajo agitación vigorosa por 3 h.

El sólido se filtró y se secó bajo vacío.

Se obtuvieron 98.1 g del producto deseado (rendimiento cuantitativo).

^1H RMN (CDCl_3): 1.96 (s, 3H, H_{10}); 1.97-3.15 (m, 4H, H_5+H_6); 2.43 (s, 3H, H_{12}); 3.81, 3.87 (2s, 6H, OCH_3); 5.35 (d, 1H, H_9); 6.76 (dd, 2H, H_2+H_3);

^{13}C RMN (CDCl_3): 19.6 (C_{11}); 20.2, 20.5 (C_5, C_6); 26.3 (C_{12}); 52.9 (C_8); 55.6, 56.0 (OCH_3); 82.9 (C_7); 108.3, 110.1 (C_2, C_3); 123.2, 125.4 ($\text{C}_{4a}, \text{C}_{8a}$); 150.7, 151.6 (C_1, C_4); 169.6 (C_{11}); 204.2 (C_9).

CCD: r.f. 0.55 (éter de petróleo/acetato de etilo = 75/25)

punto de fusión = 128-138°C.

$[\alpha]_D^{25} = -16.2^\circ$ (c=1.0, CH_2Cl_2).

Ejemplo 4

Síntesis de VI

A una solución de cloroacetato (97.3 g) en tolueno (2 l) se agregaron AIBN (1.5g) y tributilestanhidruro (225 ml) en corriente de nitrógeno. La mezcla se agitó bajo la luz de una

lámpara wolfram de 200 Watt por 24 h y posteriormente se extrajo con agua (500 ml). La fase orgánica se separó, se secó y se evaporó al vacío. El residuo se trató con ciclohexano (500 ml) con agitación, se filtró y se secó al vacío a 40°C.

- 5 Se obtuvieron 67.8 g del producto deseado en la forma de un sólido blanco.

Rendimiento: 80.3%.

^1H RMN (CDCl_3): 1.95, 2.50 (2m, 2H, H_6); 2.05 (1.3H, H_{10});

2.22 (1.3H, H_{12}); 2.40, 2.90 (2m, 2H, H_5); 3.00 (dd, 2H, H_8);

- 10 3.77, 3.80 (2s, 6H, OCH_3); 6.66 (m, 2H, $\text{H}_2 + \text{H}_3$);

^{13}C RMN (CDCl_3): 19.5, 21.0 (C_5, C_6); 24.0 (C_{10}); 26.7 (C_{12});

30.2 (C_8); 55.6, 55.5 (OCH_3); 83.6 (C_7); 107.0, 107.2 (C_2, C_3);

122.7, 125.1 ($\text{C}_{4a}, \text{C}_{8a}$); 150.9, 151.4 (C_1, C_4); 170.5 (C_{11});

206.5 (C_9).

- 15 CCD: r.f. 0.28 (tolueno/acetato de etilo = 95/5)

CLAR: r.t. = 7.4 min (Condiciones: Lichrospher 100 RP 18

(5 μm) 250x4mm $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ + 0.1% TFA = 60/40; 1ml/min; $\lambda=214\text{nm}$;

20 μl de una solución 1.2 mg/10 ml).

punto de fusión = 110-118°C.

- 20 $[\alpha]_D^{25} = -46.3^\circ$ (c=1.0, CHCl_3).

Ejemplo 5

Síntesis de I

A una solución de acetato (66 g) en metanol (5 l) se agregó una resina Amberlite IRA-400 (OH) (183 ml) previamente

activada por tratamiento con NaOH al 30% (8 x 400 ml) y se lavó con agua (5 x 400 ml) y metanol (4x400 ml). La mezcla de reacción se agitó por una noche a temperatura ambiente. Después de la separación de la resina por filtración y
 5 evaporación del solvente al vacío se obtuvo un residuo sólido el cual después de la cristalización a partir de ciclohexano/acetato de etilo, filtración y secado dio 51.85 g del producto deseado.

Rendimiento: 92%.

10 ^1H RMN (CDCl_3): 1.89 (m, 2H, H_6); 2.33 (s, 3H, H_{10}); 2.91 (m, 4H, $\text{H}_5 + \text{H}_8$); 3.65 (s, 1H, OH); 3.77, 3.80 (2s, 6H, OCH_3); 6.66 (s, 2H, $\text{H}_2 + \text{H}_3$);
 ^{13}C RMN (CDCl_3): 19.2 (C_5); 23.9 (C_{10}); 29.7, 32.4 (C_6, C_8); 55.5, 55.6 (OCH_3); 76.4 (C_7); 107.0, 107.4 (C_2, C_3); 122.7, 125.5 ($\text{C}_{1a}, \text{C}_{8a}$); 151.1, 151.6 (C_1, C_4); 212.3 (C_9).

15 CCD: r.f. 0.27 (éter de petróleo/acetato de etilo = 80/20)

CLAR: r.t. = 5.9 min (Condiciones: Lichrospher 100 RP 18 (5 μm) 250x4mm $\text{CH}_3\text{CN}/\text{H}_2\text{O}$ + 0.1% TFA = 50/50; 1ml/min; $\lambda=214\text{nm}$; 20 μl de una solución 2.5 mg/ml).

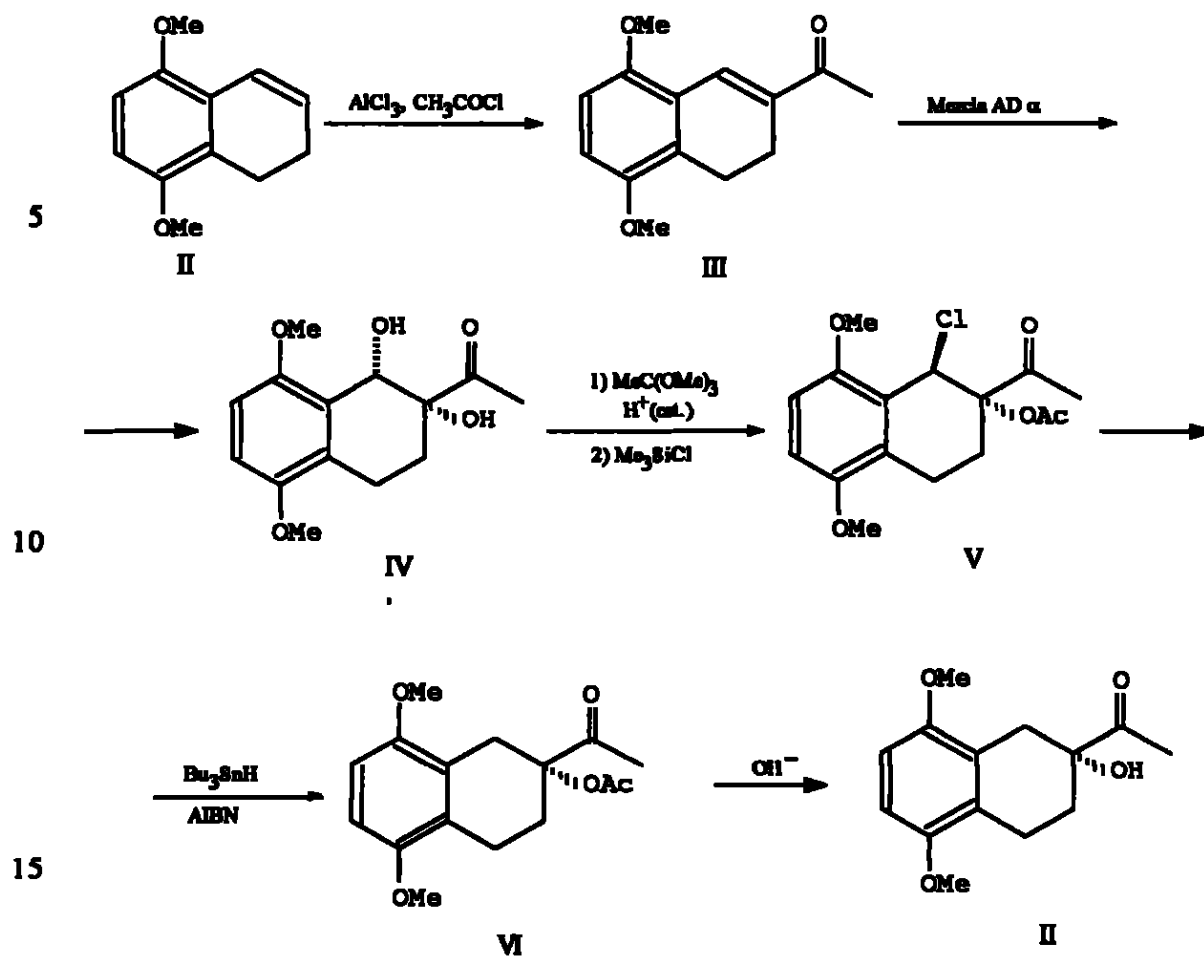
e.e = > 99% determinado por CLAR quiral (Condiciones:

20 Quiralcel OD 250 x 4.6 mm; n-hexano/EtOH = 90/10; 1 ml/min; $\lambda=214\text{ nm}$; 20 μl de una solución 1.35 mg/10 ml).

punto de fusión = 126-129°C.

$[\alpha]_D^{25} = -46.2^\circ$ (c=1.0, CHCl_3).

ESQUEMA DE REACCIÓN I

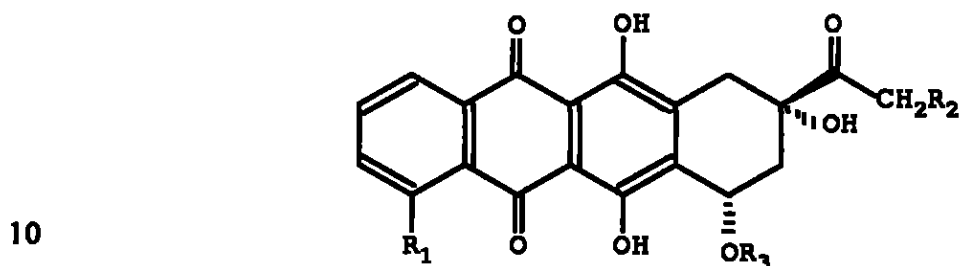


Se hace constar que con relación a esta fecha, el mejor método conocido por la solicitante para llevar a cabo la citada invención, es el que resulta claro de la presente descripción de la invención

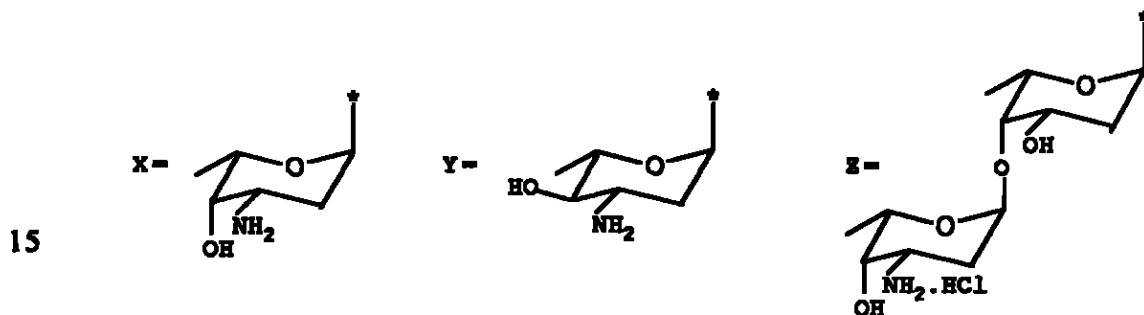
REIVINDICACIONES

Habiéndose descrito la invención como antecede se reclama como propiedad lo contenido en las siguientes reivindicaciones:

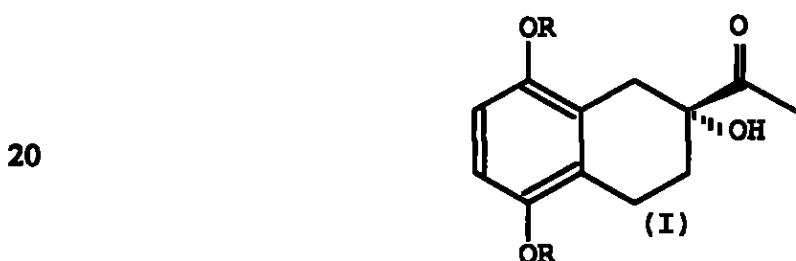
- 5 1. Proceso para la preparación de antraciclinas de fórmula VIII:



en donde $R_1 = H, OH, OCH_3$; $R_2 = H, OH$; $R_3 = X, Y$ o Z donde

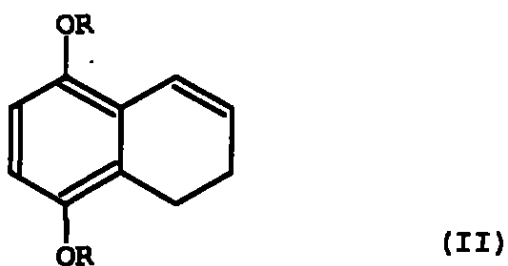


que comprende la formación del intermediario de fórmula (I)



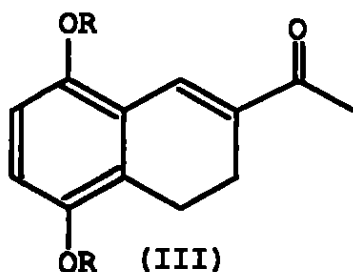
25 en donde: R = alquilo de 1 a 3 átomos de carbono
caracterizado porque el intermediario de fórmula (I) se
prepara a partir de un 5,8-dialcoxi-3,4-dihidronaftaleno de
fórmula (II):

19



5 en donde R = alquilo de 1 a 3 átomos de carbono
conforme a los siguientes pasos:

a) el 5,8-dialcoxi-3,4-dihidronaftaleno de fórmula (II) se
acila en un solo paso con cloruro de acetilo en la presencia
de un exceso de AlCl_3 a una temperatura comprendida entre -
10 35°C y 25°C , formando el derivado de acilo (III)
correspondiente

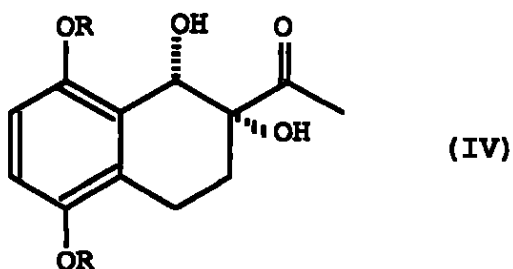


15

en donde R = alquilo de 1 a 3 átomos de carbono;

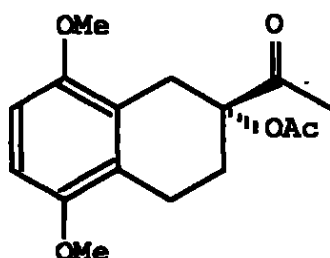
b) el derivado de acilo (III) se hidroxila
enanatiosselectivamente con una cantidad catalítica de osmio,
para formar el diol (IV)

20



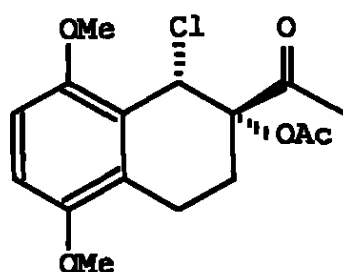
25 en donde R = alquilo de 1 a 3 átomos de carbono;

c) el diol (IV) se convierte en el acetato (VI)



5

mediante reducción directa o alternativamente, a través del cloroacetato (V)

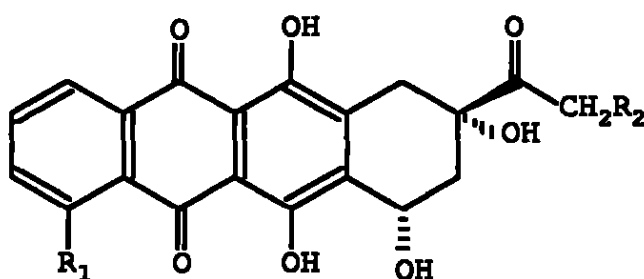


10

por reacción con trietilortoacetato y trimetilsililcloruro seguido por una reducción conforme a procedimientos conocidos;

15 d) el acetato (VI) se hidroliza a la tetralina de fórmula (I).

2. Proceso de conformidad con la reivindicación 1, caracterizado porque la tetralina de fórmula (I) es convertida, conforme a procedimientos conocidos, en la
20 antraciclina de fórmula (VII),



25

en donde $R_1 = H, OH, OCH_3$ y $R_2 = H, OH, O\text{-acilo}$, en donde el grupo acilo se selecciona de entre formilo, acetilo, mono- o di-cloroacetilo,

y ésta es finalmente convertida en la antraciclina de fórmula
5 (VIII) como se definió en la reivindicación 1, conforme a procedimientos conocidos.

3. Proceso de conformidad con las reivindicaciones 1 y 2, caracterizado porque $R = \text{metilo}$ y $R_2 = O\text{-acetilo}$.

4. Proceso de conformidad con la reivindicación 1,
10 caracterizado porque la acilación se lleva a cabo a 0°C .

5. Proceso de conformidad con la reivindicación 1, caracterizado porque la dihidroxilación enantioselectiva de acuerdo al paso (b) se lleva a cabo usando cantidades catalíticas de osmio usando la mezcla AD- α reactiva con una
15 adición complementaria de una sal de osmio y metansulfonamida.

6. Proceso de conformidad con la reivindicación 5, caracterizado porque la sal de sodio usada es $K_2OsO_2(OH)_4$.

7. Proceso de conformidad con la reivindicación 6,
20 caracterizado porque la reacción se lleva a cabo a -4°C a $+20^\circ\text{C}$.

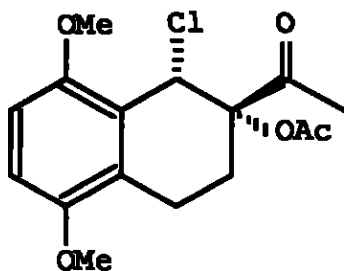
8. Proceso de conformidad con la reivindicación 7, caracterizado porque la reacción se lleva a cabo a 0°C .

9. Proceso de conformidad con las reivindicaciones 1 a
25 8, caracterizado porque las antraciclinas de fórmula (VIII)

son daunomicina (VIII, en donde: $R_1=\text{OCH}_3$, $R_2=\text{H}$, $R_3=\text{X}$),
doxorubicina (VIII, en donde: $R_1=\text{OCH}_3$, $R_2=\text{OH}$, $R_3=\text{X}$),
hidrarubicina (VIII, en donde: $R_1=\text{H}$, $R_2=\text{H}$, $R_3=\text{X}$), epirubicina
(VIII, en donde: $R_1=\text{OCH}_3$, $R_2=\text{OH}$, $R_3=\text{Y}$), o una tetraciclina de
5 fórmula VIII en donde: $R_1=\text{H}$, $R_2=\text{OH}$, $R_3=\text{Z}$, en donde X, Y y Z
son como se definieron en la reivindicación 1.

10. El compuesto ópticamente activo de fórmula (V)

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(V)

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RESUMEN DE LA INVENCION

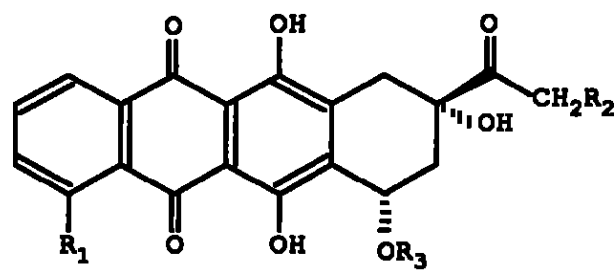
Se describe un proceso para la síntesis de antraciclinas ópticamente activas caracterizado por el hecho de que el intermediario clave 5,8-dialcoxi(R)-2-acetil-2-hidroxi-
5 1,2,3,4-tetrahidronaftaleno se prepara a partir de 5,8-dialcoxi-3,4-dihidronaftaleno mediante acilación, dihidroxilación asimétrica, transformación en cloroacetato, deshidrocloración e hidrólisis final.

REIVINDICACIONES

1. Proceso para la preparación de antraciclinas de fórmula

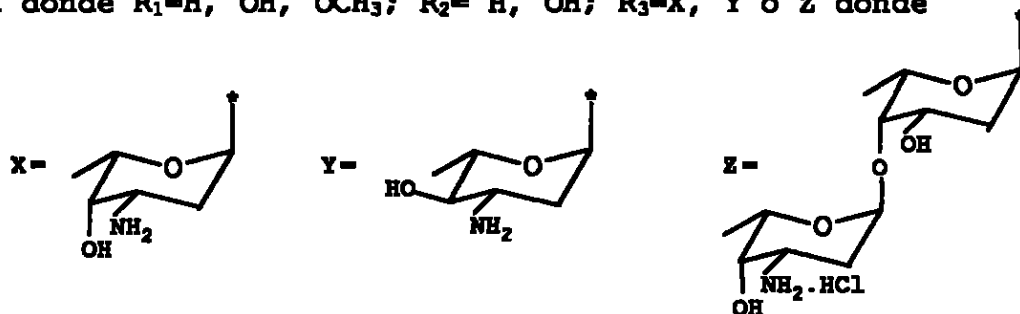
VIII:

5



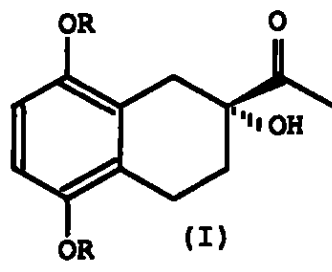
en donde $R_1 = H, OH, OCH_3$; $R_2 = H, OH$; $R_3 = X, Y$ o Z donde

10



que comprende la formación del intermediario de fórmula (I)

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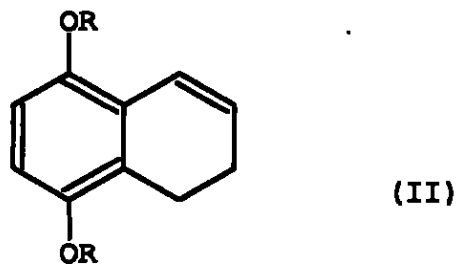


en donde: $R =$ alquilo de 1 a 3 átomos de carbono

caracterizado porque el intermediario de fórmula (I) se prepara

20 a partir de un 5,8-dialcoxi-3,4-dihidronaftaleno de fórmula

(II):

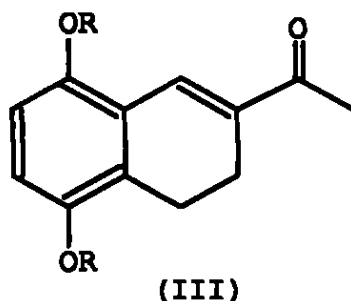


en donde R = alquilo de 1 a 3 átomos de carbono

conforme a los siguientes pasos:

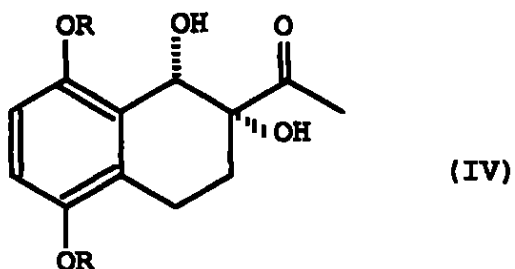
- a) el 5,8-dialcoxi-3,4-dihidronaftaleno de fórmula (II) se acila en un solo paso con cloruro de acetilo en la presencia de un exceso de AlCl_3 a una temperatura comprendida entre -35°C y 25°C , formando el derivado de acilo (III) correspondiente

10



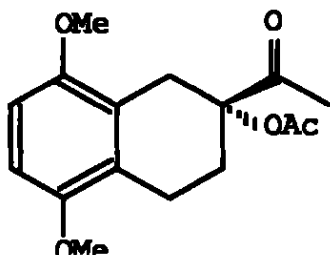
en donde R = alquilo de 1 a 3 átomos de carbono;

- b) el derivado de acilo (III) se hidroxila enantioselectivamente con una cantidad catalítica de osmio, para formar el diol (IV)

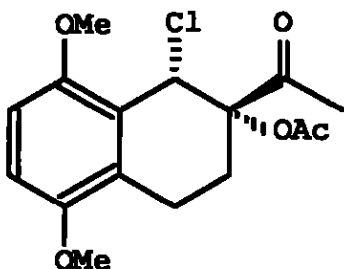


20 en donde R = alquilo de 1 a 3 átomos de carbono;

- c) el diol (IV) se convierte en el acetato (VI)

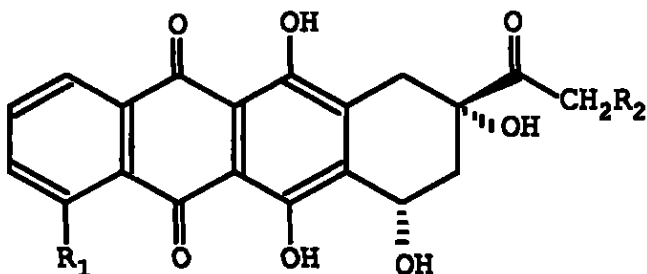


mediante reducción directa o alternativamente, a través del cloroacetato (V)



por reacción con trietilortoacetato y trimetilsililcloruro seguido por una reducción conforme a procedimientos conocidos; d) el acetato (VI) se hidroliza a la tetralina de fórmula (I).

2. Proceso de conformidad con la reivindicación 1, caracterizado porque la tetralina de fórmula (I) es convertida, conforme a procedimientos conocidos, en la antraciclina de fórmula (VII),



en donde $R_1 = H, OH, OCH_3$ y $R_2 = H, OH, O\text{-acilo}$, en donde el grupo acilo se selecciona de entre formilo, acetilo, mono- o di-cloroacetilo, y ésta es finalmente convertida en la antraciclina de fórmula (VIII) como se definió en la reivindicación 1, conforme a procedimientos conocidos.

3. Proceso de conformidad con las reivindicaciones 1 y 2, caracterizado porque R = metilo y R₂ = O-acetilo.

4. Proceso de conformidad con la reivindicación 1, caracterizado porque la acilación se lleva a cabo a 0°C.

5 5. Proceso de conformidad con la reivindicación 1, caracterizado porque la dihidroxilación enantioselectiva de acuerdo al paso (b) se lleva a cabo usando cantidades catalíticas de osmio usando la mezcla AD-α reactiva con una adición complementaria de una sal de osmio y metansulfonamida.

10 6. Proceso de conformidad con la reivindicación 5, caracterizado porque la sal de sodio usada es K₂OsO₂(OH)₄.

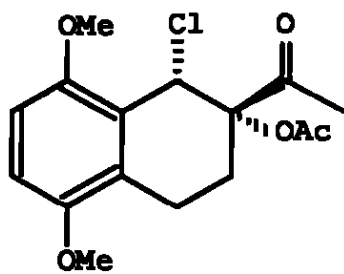
7. Proceso de conformidad con la reivindicación 6, caracterizado porque la reacción se lleva a cabo a -4°C a +20°C.

15 8. Proceso de conformidad con la reivindicación 7, caracterizado porque la reacción se lleva a cabo a 0°C.

9. Proceso de conformidad con las reivindicaciones 1 a 8, caracterizado porque las antraciclinas de fórmula (VIII) son daunomicina (VIII, en donde: R₁=OCH₃, R₂=H, R₃=X), doxorubicina (VIII, en donde: R₁=OCH₃, R₂=OH, R₃=X), hidrarubicina (VIII, en donde: R₁=H, R₂=H, R₃=X), epirubicina (VIII, en donde: R₁=OCH₃, R₂=OH, R₃=Y), o una tetraciclina de fórmula VIII en donde: R₁=H, R₂=OH, R₃=Z, en donde X, Y y Z son como se definieron en la reivindicación 1.

20

10. El compuesto ópticamente activo de fórmula (V)



(V)

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101

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Trámite : 011 PCT-PATENT 379 FASE NNCI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION ✓ MODELO DE UTILIDAD	(✓)	()
- Indicación de que se solicita la concesión de una patente.	(✓)	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	(✓)	()
- Descripción de la invención.	(✓)	()
- Dibujos de ser estos pertinentes.	(✓)	()
- Comprobante de Pago de las tasas establecidas.	(✓)	()
COMPLETA () INCOMPLETA ()		
DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA () INCOMPLETA ()		
ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA () INCOMPLETA ()		

Firma Responsable: **ANDREA ROSPE**

Fecha: